Basic Principles in Supramolecular Chemistry

Prof. Dr. Christoph A. Schalley

FU Berlin

The Non-covalent Bond

Electrostatic Interactions: Interaction Energies

charge-charge

$$U = \frac{q_1 q_2}{4\pi\varepsilon\varepsilon_0 r}$$

charge-dipole
(fixed dipole)

$$U = -\frac{q\mu\cos\theta}{4\pi\varepsilon\varepsilon_0 r^2}$$

charge-dipole
(free dipole rotation)

$$U = -\frac{q^2\mu^2}{6(4\pi\varepsilon\varepsilon_0)^2 kTr^4}$$

dipole-dipole
(fixed dipoles)

$$U = -\frac{\mu_1\mu_2}{4\pi\varepsilon\varepsilon_0 r^3}(2\cos\theta_1\cos\theta_2 - \sin\theta_1\cos\phi\sin\theta_2)$$

dipole-dipole
(free dipole rotation)

$$U = -\frac{\mu_1^2\mu_2^2}{3(4\pi\varepsilon\varepsilon_0)^2 kTr^6}$$

U: interaction energy
q: charge
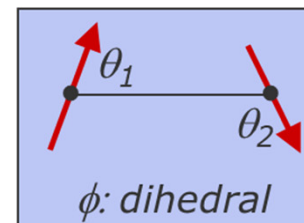μ: dipole moment
ε: medium dielectric constant
ε_0: vacuum permittivity
  ($\varepsilon_0 = 8.85 \cdot 10^{-12}$ $C^2N^{-1}m^{-2}$)
r: distance
θ, ϕ: angles (see below)
k: Boltzmann constant
T: temperature

θ_1
θ_2
ϕ: dihedral

Important Factor: The Dielectric Constant ε

Association constants and ion-pair interaction enthalpies for tetra(n-butyl)ammonium perchlorate

solvent	ε	K_a (l mol^{-1})	$-\Delta G$ (kJ mol^{-1})
vacuum	1.0	not available	
dioxane	2.2	ca. 10^{19}	109
benzene	2.3	$3 \cdot 10^{17}$	100
anisole	4.4	10^9	52
1,2-dichloroethane	10.1	6,500	22
1-butanol	20.4	2,200	19
acetone	20.7	200	13
acetonitrile	37.5	53	10
water	78.4	no ion pair formation	

Hydrogen Bonds

some properties of hydrogen bonds

	strong	*moderate*	*weak*
A-H•••B interaction	mainly covalent	mainly electrostatic	electrostatic
bond energy ($kJ\,mol^{-1}$)	60 - 160	15 - 60	< 12
bond lengths (Å)			
H•••B	1.2 - 1.5	1.5 -2.2	2.2 - 3.2
A•••B	2.2 - 2.5	2.5 -3.2	3.2 - 4.0
bond angles (°)	175 - 180	130 - 180	90 - 150
^{1}H NMR shifts (Δppm)	14 - 22	< 14	
IR vibration shifts (%)	25 %	10 - 25 %	< 10 %

strongest hydrogen bond known: F^{-}•••H-F (> 160 kJ/mol)

Secondary Effects in Hydrogen Bonding
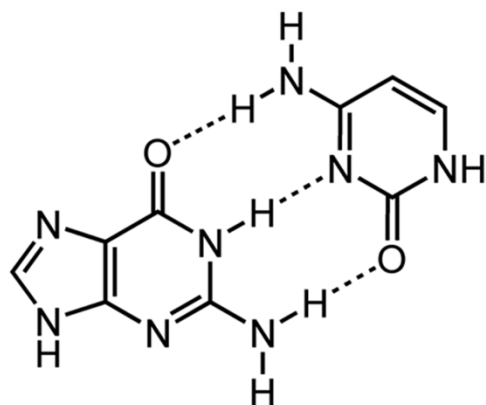
DDA•AAD
$-\Delta G^o = 22.1$ kJ mol^{-1}
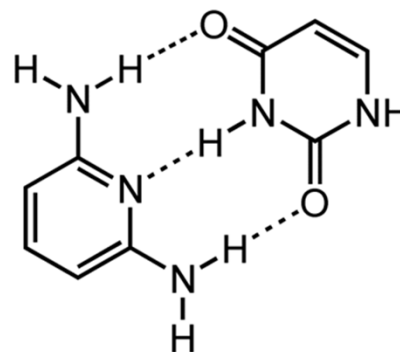
DAD•ADA
$-\Delta G^o = 11.4$ kJ mol^{-1}

"stabilizing"
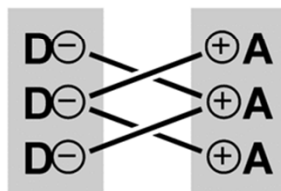
4 attractive
secondary
interactions

"neutral"
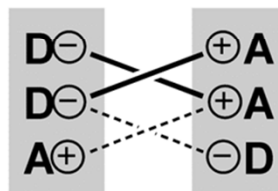
2 attractive, 2 repulsive
secondary
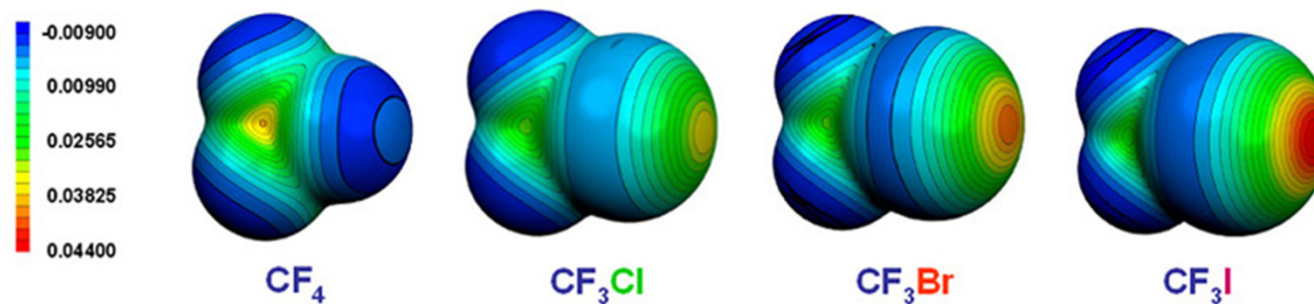interactions

"destabilizing"
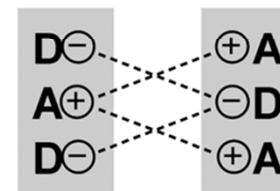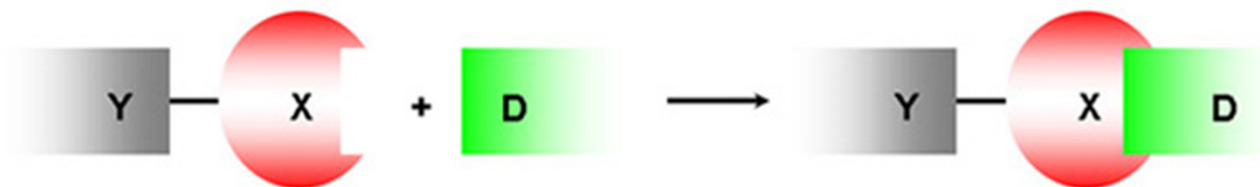
4 repulsive
secondary
interactions

The Halogen Bond

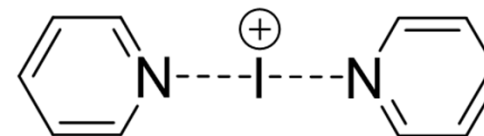electron density around the Cl, Br and I nucleus is anisotropic

highly directional: Y-X···D angle very close to 180°

strong, symmetric coordinative **XB** with iodonium ions

T. Clark, M. Hennemann, J. S. Murray, P. Politzer, *J. Mol. Model.* **2007**, *13*, 291; A. C. C. Carlsson, J. Gräfenstein, A. Budnjo, J. L. Laurila, J. Bergquist, A. Karim, R. Kleinmaier, U. Brath, M. E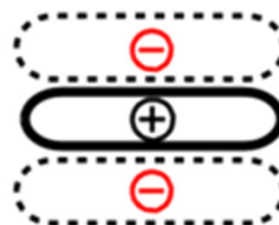rdélyi, *J. Am. Chem. Soc.* **2012**, *134*, 5706–5715. Figures taken from: http://www.halogenbonding.eu/halogenbonding.php [**12.10.2015**].

Non-Covalent Interactions with Aromatic Rings
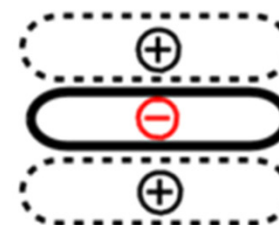
Quadrapole Moments

Benzene

Hexafluorobenzene
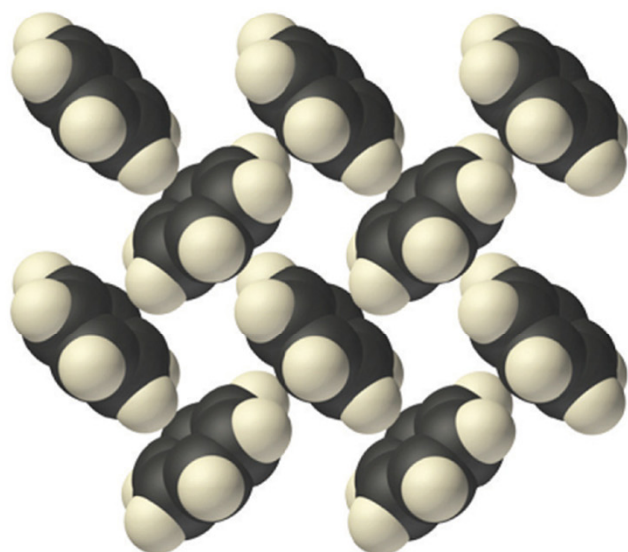
edge-to-face interaction:
benzene crystal structure (m.p. 5.5°C)

face-to-face interaction:
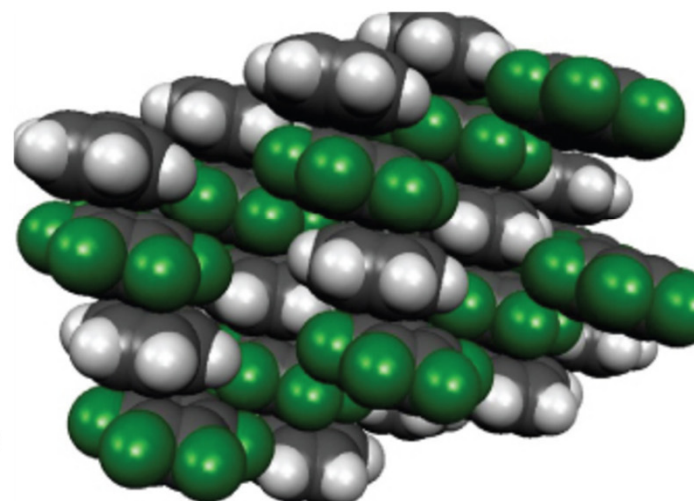crystal structure of 1:1 benzene:hexafluorobenzene
(m.p. 23°C)

Cation-π Interactions

in solution still under debate, often postulated to play a role in protein folding

| cation	molecule	ΔH (kJ mol^{-1})
Li$^+$	C_6H_6	160.1
Na$^+$	C_6H_6	117.0
K$^+$	C_6H_6	79.4
K$^+$(benzene)	C_6H_6	75.2
K$^+$(benzene)$_2$	C_6H_6	60.2
K$^+$(benzene)$_3$	C_6H_6	52.7
K$^+$	H_2O	74.8
NH$_4^+$	1,4-$C_6H_4F_2$	54.3 [a]
NH$_4^+$	C_6H_5F	60.2 [a]
NH$_4^+$	C_6H_6	80.7

question: why is KCl so well soluble in water, but not in benzene, although the interaction energies of the potassium ion with both solvent molecules are so similar?

The Hydrophobic Effect: Cyclodextrin Complexes

α-cyclodextrin

β-cyclodextrin
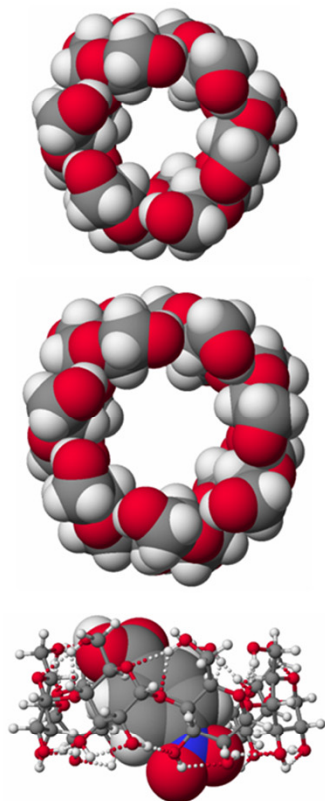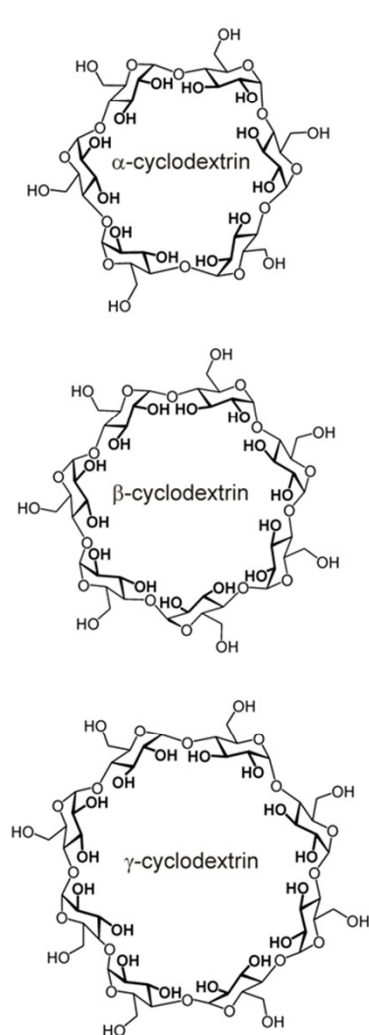
γ-cyclodextrin

α-CD: d_{in} = 0.57 nm
d_{out} = 1.37 nm

β-CD: d_{in} = 0.78 nm
d_{out} = 1.53 nm

γ-CD: d_{in} = 0.95 nm
d_{out} = 1.69 nm

examples for solution-phase guests, which have been studied as intact cyclodextrin complexes by mass spectrometry
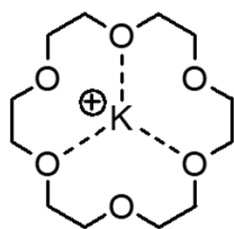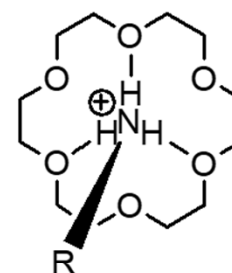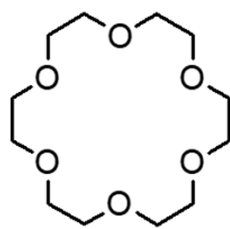
propanolol

nipradilol

nileprost

piroxicam

terfenadine

ketoconazole
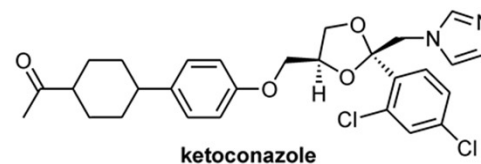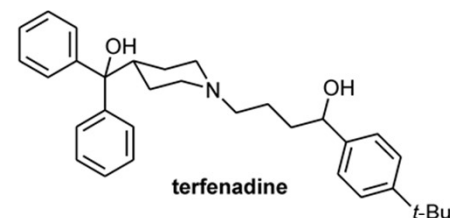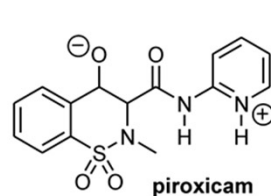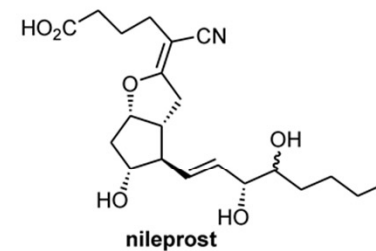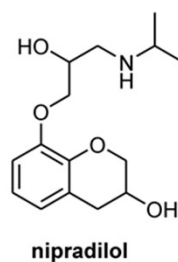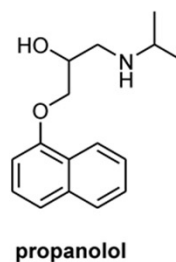
Molecular Recognition, Complementarity, and the Principle of Preorganization
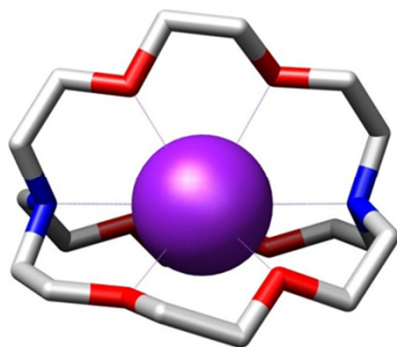
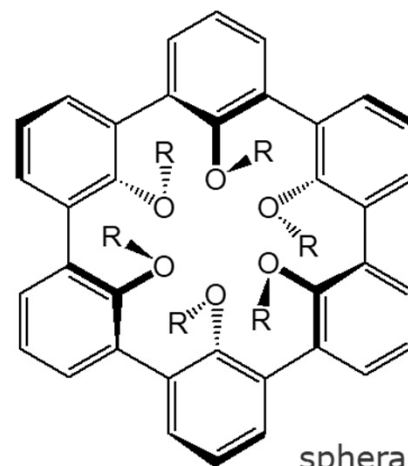# Molecular Recognition: Typical Host Molecules I

Crown Ethers

alkali metal ion binding

ammonium ion binding

cryptands
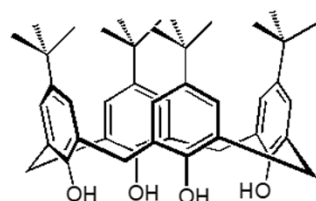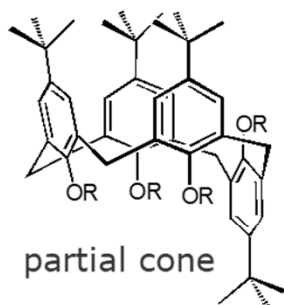
spherands

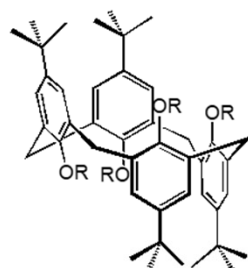# Molecular Recognition: Typical Host Molecules II

Calix[4]arene
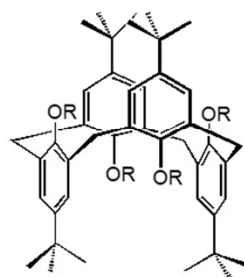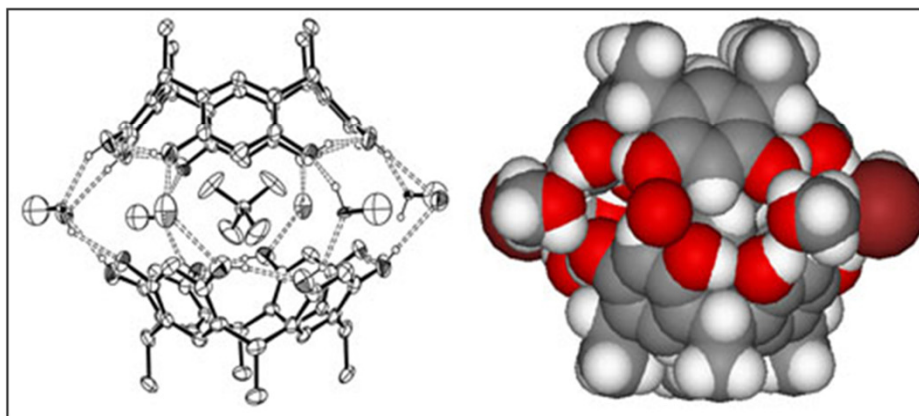

cone

partial cone

1,3-alternate
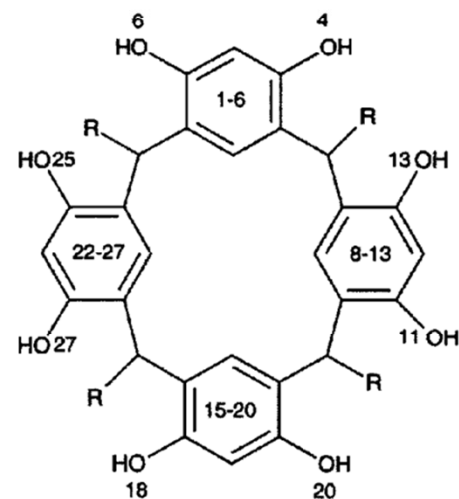
1,2-alternate

Resorcin[4]arene
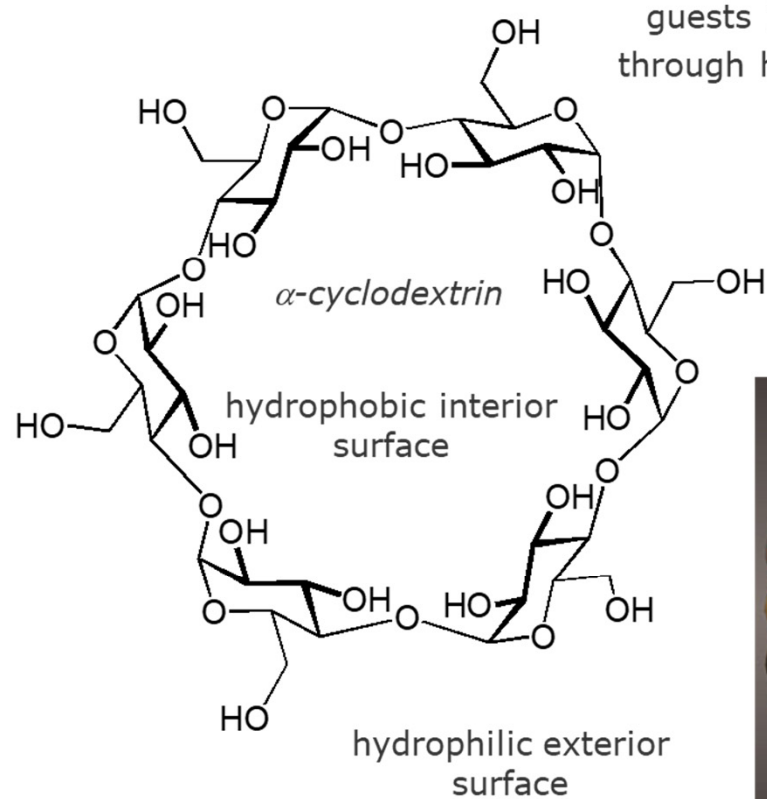
good cation binders through cation-π interactions

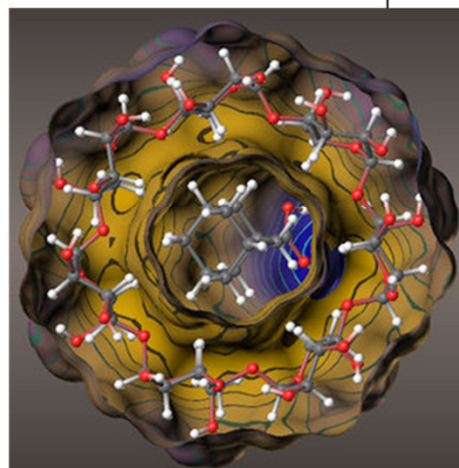crystal structure of a resorcinarene capsule filled with tetramethyl ammonium ions

Cyclodextrins

inclusion of hydrophobic
guests inside the cavity
through hydrophobic effect

model of β-cyclodextrin

α-cyclodextrin

hydrophobic interior
surface

hydrophilic exterior
surface
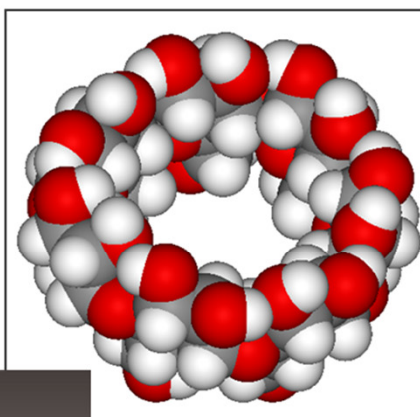
Molecular Recognition: Complementarity of Host and Guest
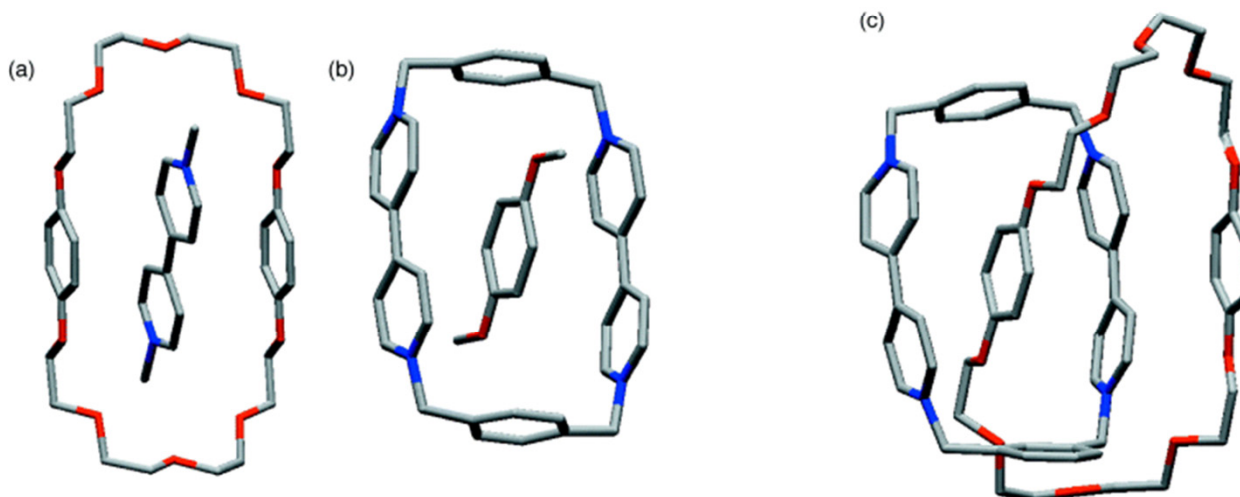
electronic complementarity: electron-poor aromatic guest interacts favorably with electron-rich host and vice versa

complementarity of binding sites: ammonium-methyl-C-H groups can form O…H-C hydrogen bonds with oxygen atoms of crown-like host

steric complementarity: guest molecule needs to fit size-wise into the cavity of the host

78%   67%   58%   48%   45%   57%
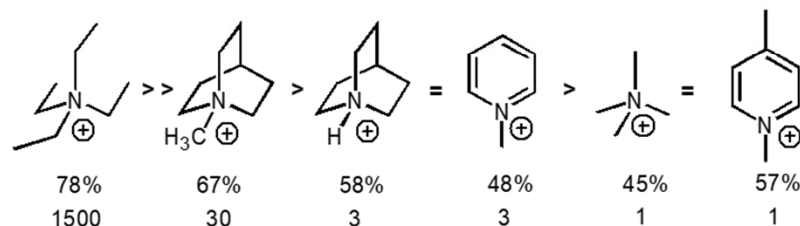1500   30   3   3   1   1
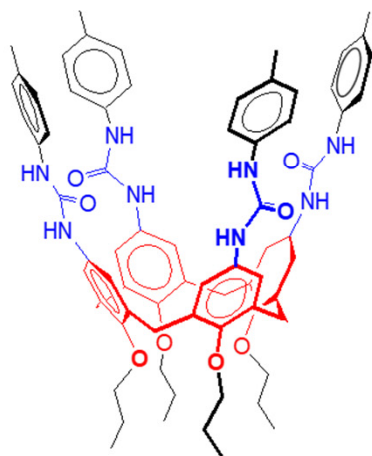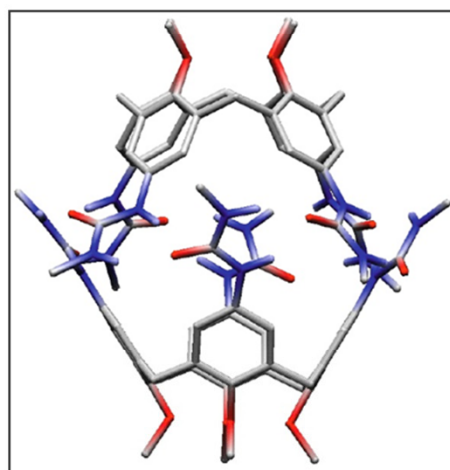
the curvature of the calixarene scaffold forces the p-systems of the aromatic rings to interact

146%   103%

keine Gäste

the electrostatic potential of the molecular surface becomes more negative inside

this provides an excellent environ-ment for cationic guests
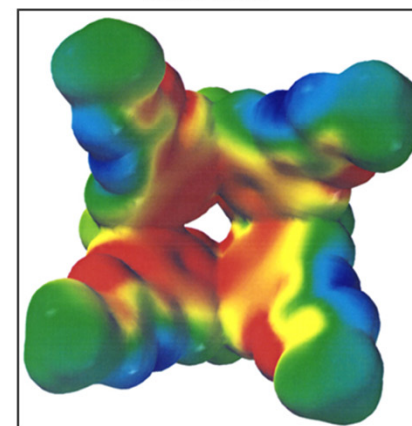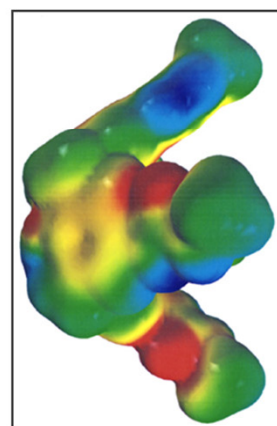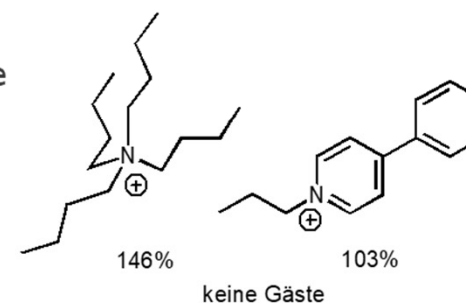
Molecular Recognition: Principle of Preorganization
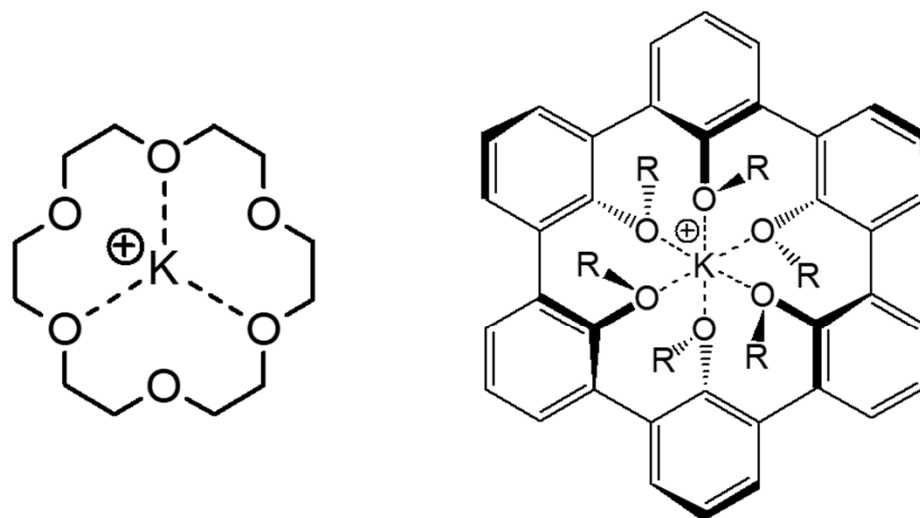
Difference in binding constants: $10^{10}*K(crown) = K(spherand)$,
which relates to a difference in binding energies of ca. 60 kJ/mol

crown ether itself is floppy, thus conformational fixation occurs upon potassium binding
(unfavorable loss of entropy)

spherand bears donor oxygens well preorganized and sterically fixed

Macrocyclic Effect, Macrobicyclic Effect, and Chelation

Chelate Effect: Oligodentate Ligands
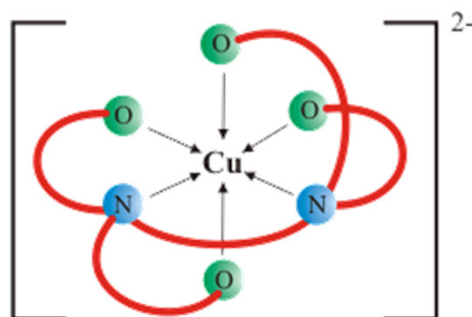
Cu²⁺/EDTA complex
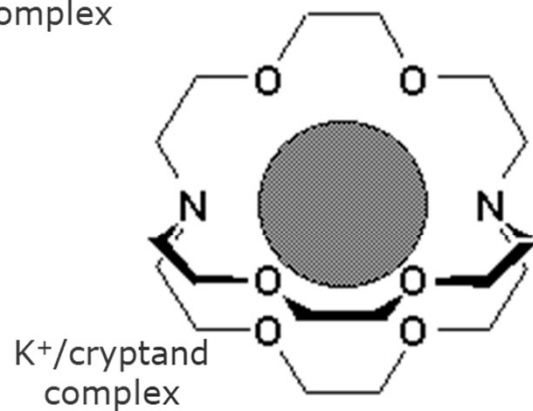
K⁺/cryptand complex
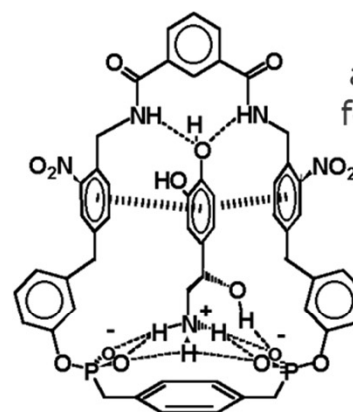
adrenaline receptor for aqueous solution
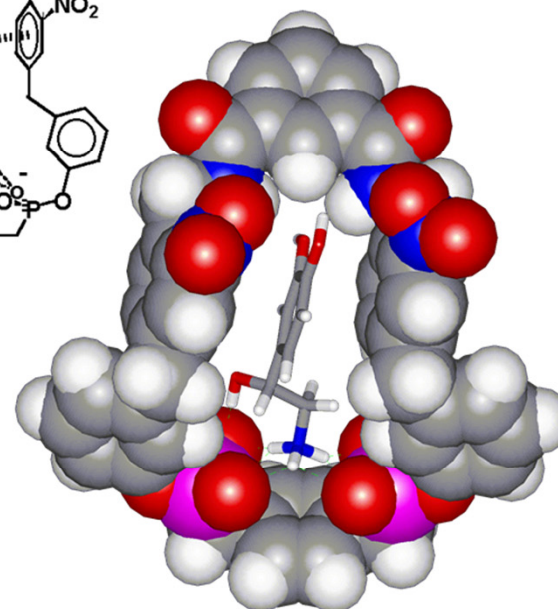
bond strength increases with the number of donor atoms

Macro(bi)cyclic Effect: Fixing Conformations
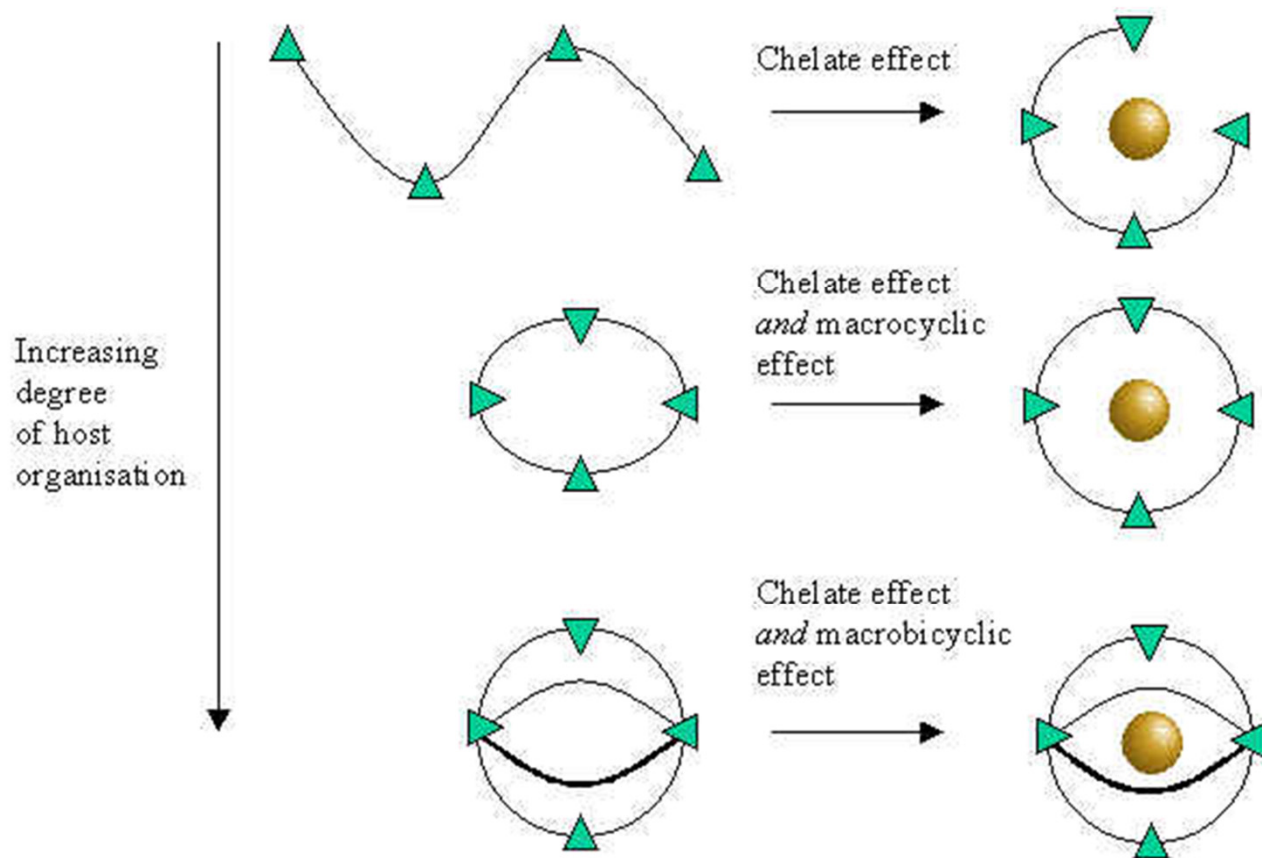
Allosteric Behavior

Allosterics: Controlling Molecular Recognition by Effectors
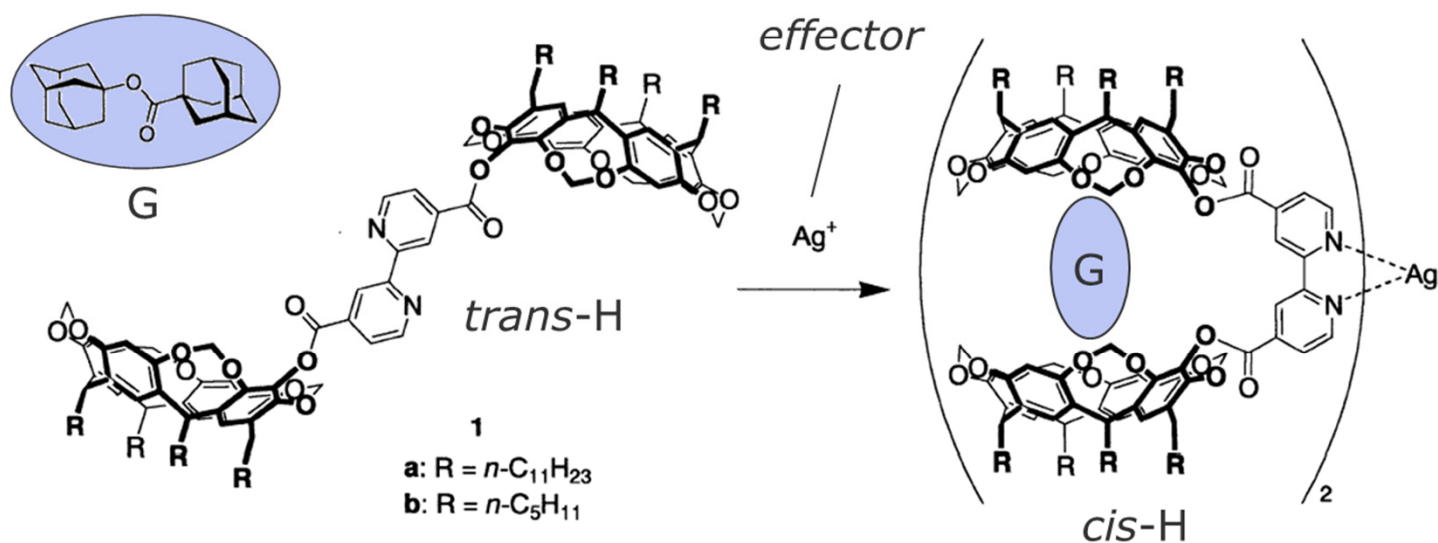
very weak binding of guest without metal ion due to transoid conformation of host (only 1 interaction possible)

stronger binding of guest with metal ion due to cisoid conformation of host (two binding sites available)

A. Lützen, O. Haß. T. Bruhn, *Tetrahedron Lett.* **2002** , *43* , 1807

Cooperativity

Oxygen-Binding to Hemoglobin: Classics in Cooperativity

oxygen bound to hemoglobin ($\alpha_2\beta_2$ tetramer) with positive cooperativity
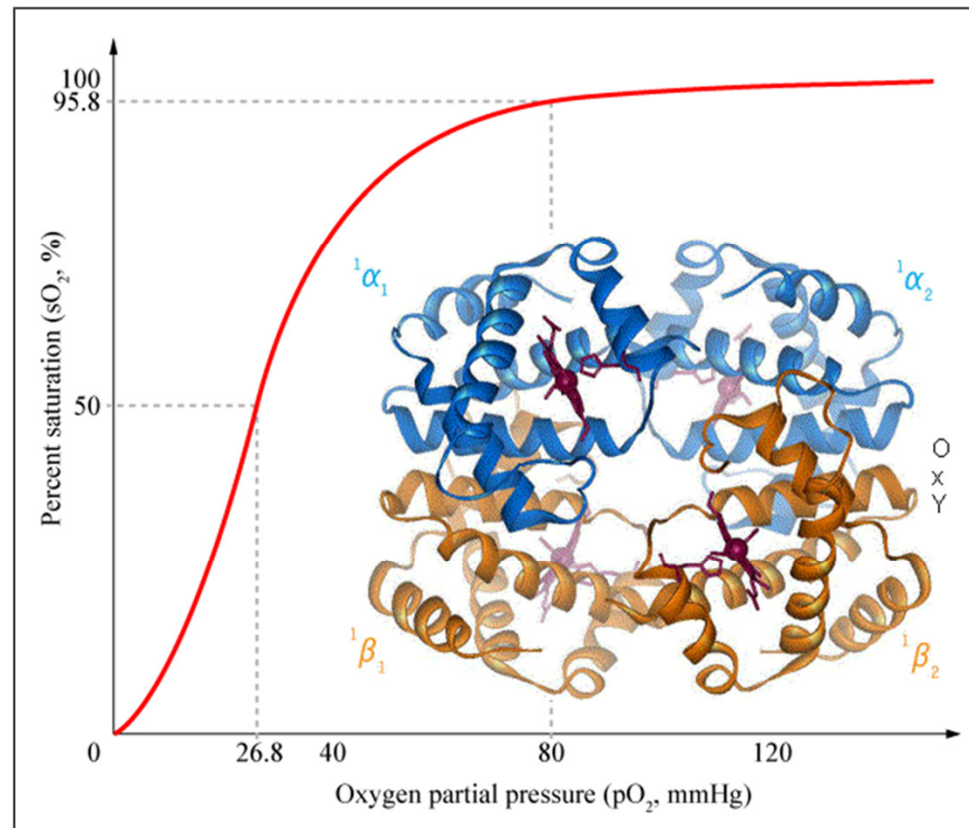
oxygen partial pressure in air under normal conditions:

21% * 760 mmHg = 160 mmHg

thus: almost full saturation of hemoglobin with O_2 under these conditions
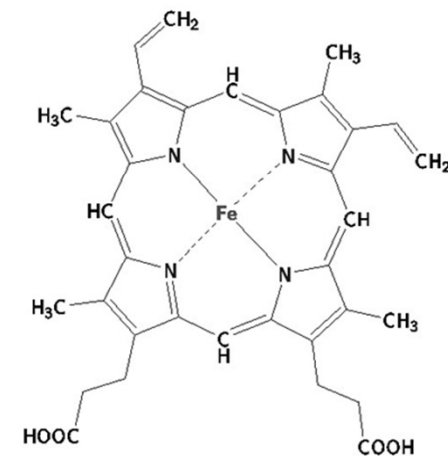
Cooperativity in Artificial Receptors

$K_a = 3.4 \times 10^4 \text{ M}^{-1}$

CuCl₂

5

5-Cu(II)

$K < 3.9 \times 10^6 \text{ M}^{-1}$

$K > 8.3 \times 10^6 \text{ M}^{-1}$

$K > 6.4 \times 10^4 \text{ M}^{-1}$

CuCl₂

5-citrate

5-Cu(II)-citrate

Multivalency

Multivalency: What is It?

"Multivalency describes the binding of two (or more) entities that involves the simultaneous interaction between multiple, complementary functionalities on these entities."

A. Mulder, J. Huskens, D. N. Reinhoudt, *Org. Biomol. Chem.* **2004**, 2, 3409

trivalent host	trivalent guest		trivalent complex
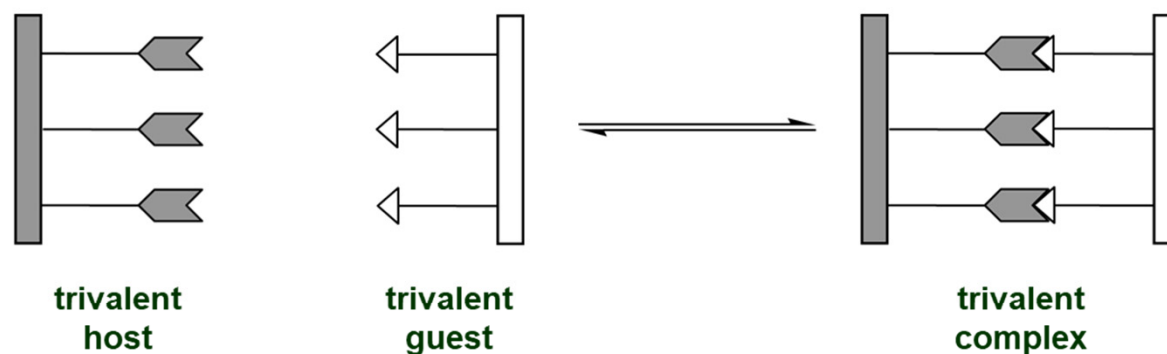
one defines the amplification factor as:
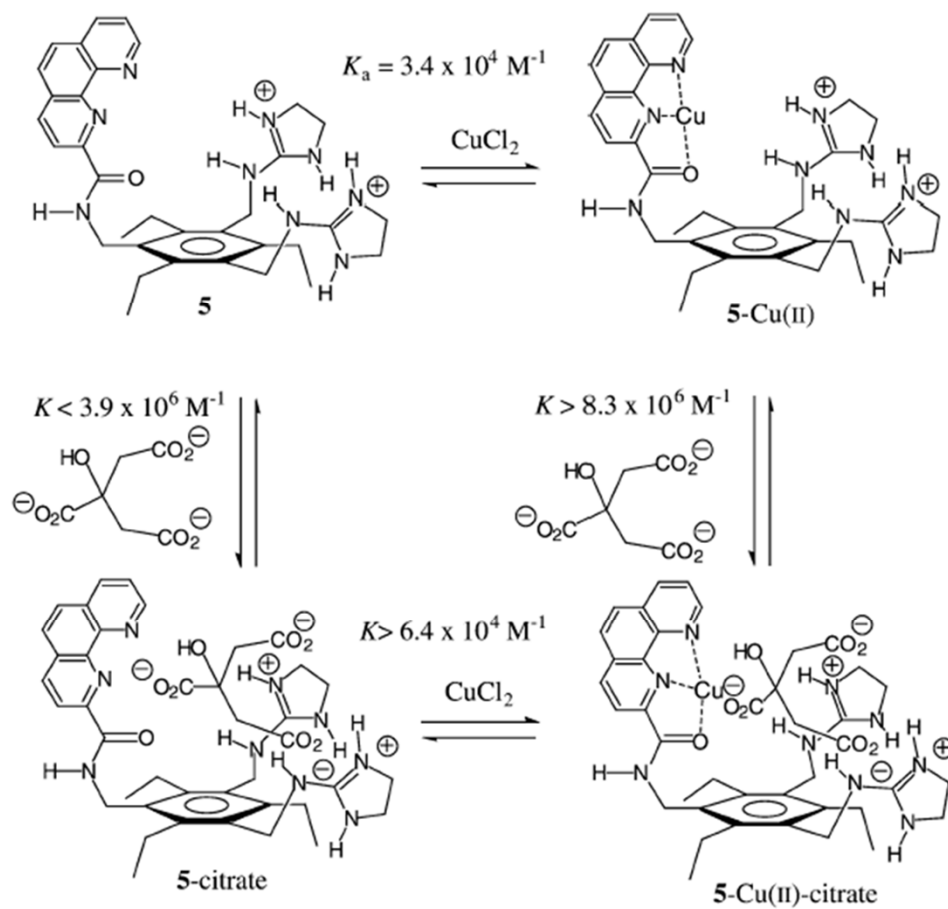
$$\beta = \frac{K^{multi}}{K^{mono}}$$

one defines the cooperativity as:

$$\alpha = \frac{\ln K^{multi}}{\ln (K^{mono})^n} = \frac{\Delta G^{multi}}{n * \Delta G^{mono}}$$

NO Multivalency if One Partner is Monovalent

For multivalency, the separation of any entity from the complex requires the dissociation of ≥ 2 interactions!

monovalent host   **monovalent guest**   **monovalent complex**

trivalent host   **3 monovalent guests**   **monovalent interactions**

K_{POLY}
CD_2Cl_2

$[3\text{-}H_3]^{3+}$

$[6 \supset 3\text{-}H_3]^{3+}$

6
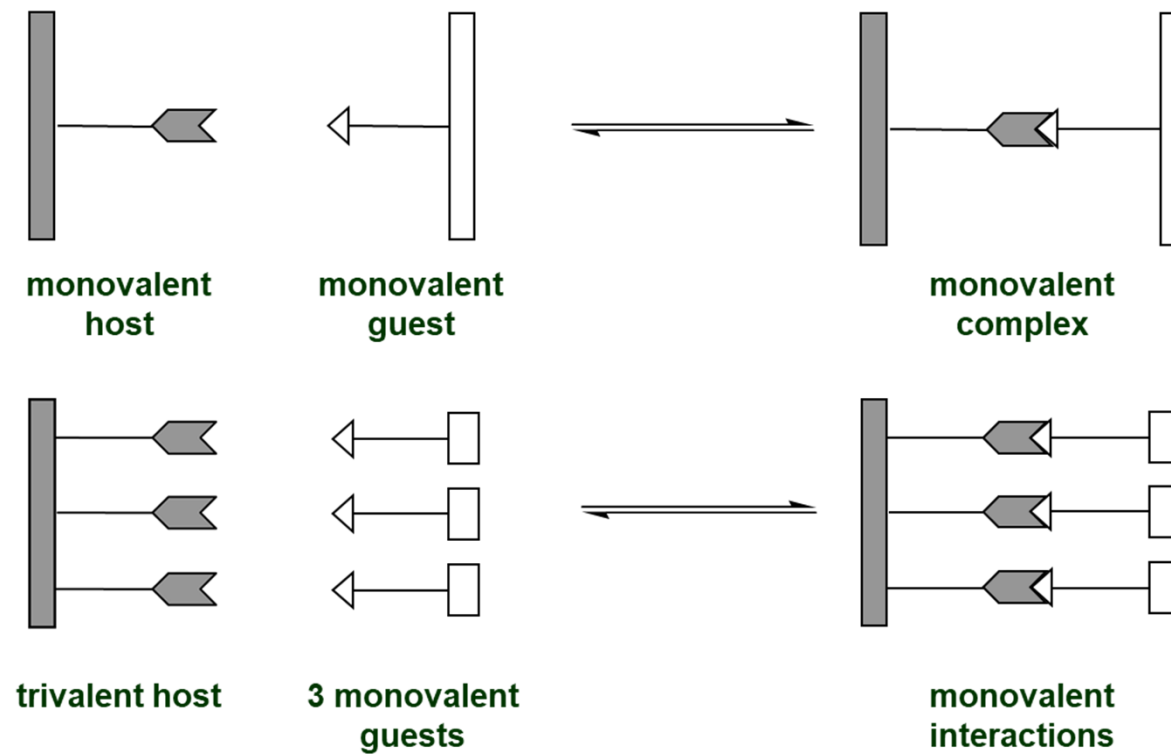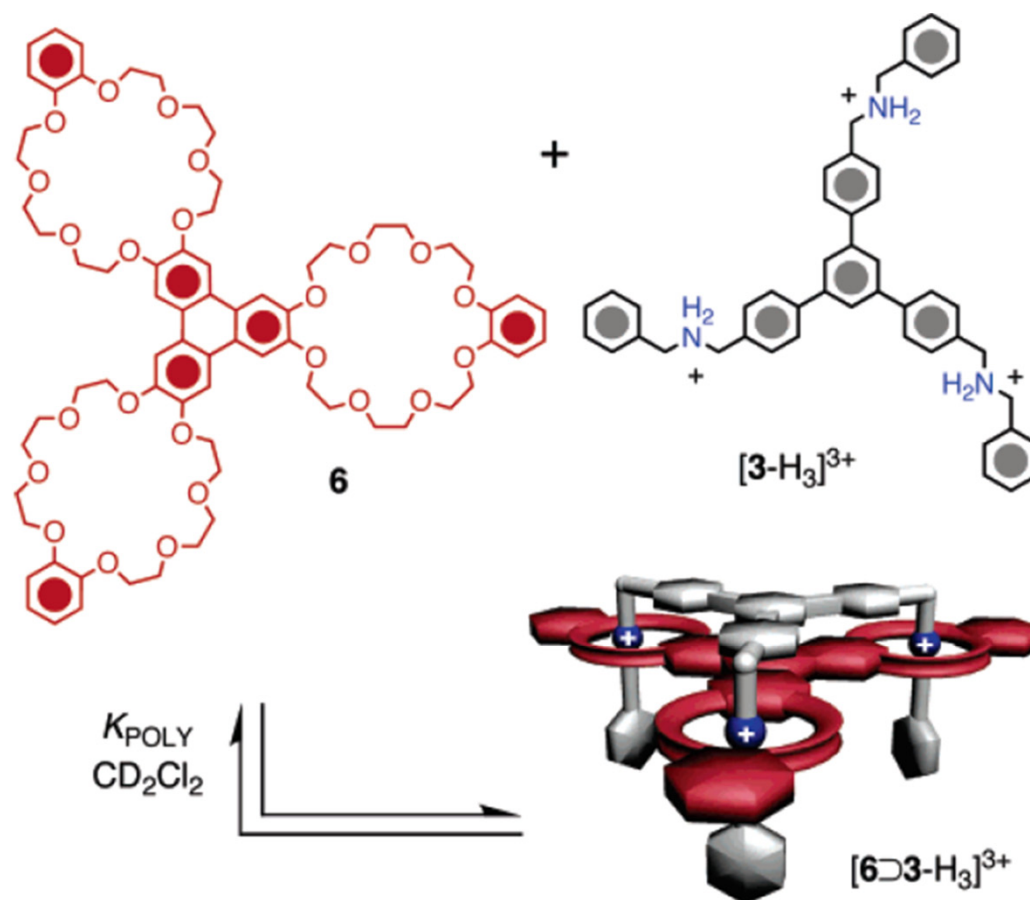
Multivalency: Mechanism of Threading Reaction
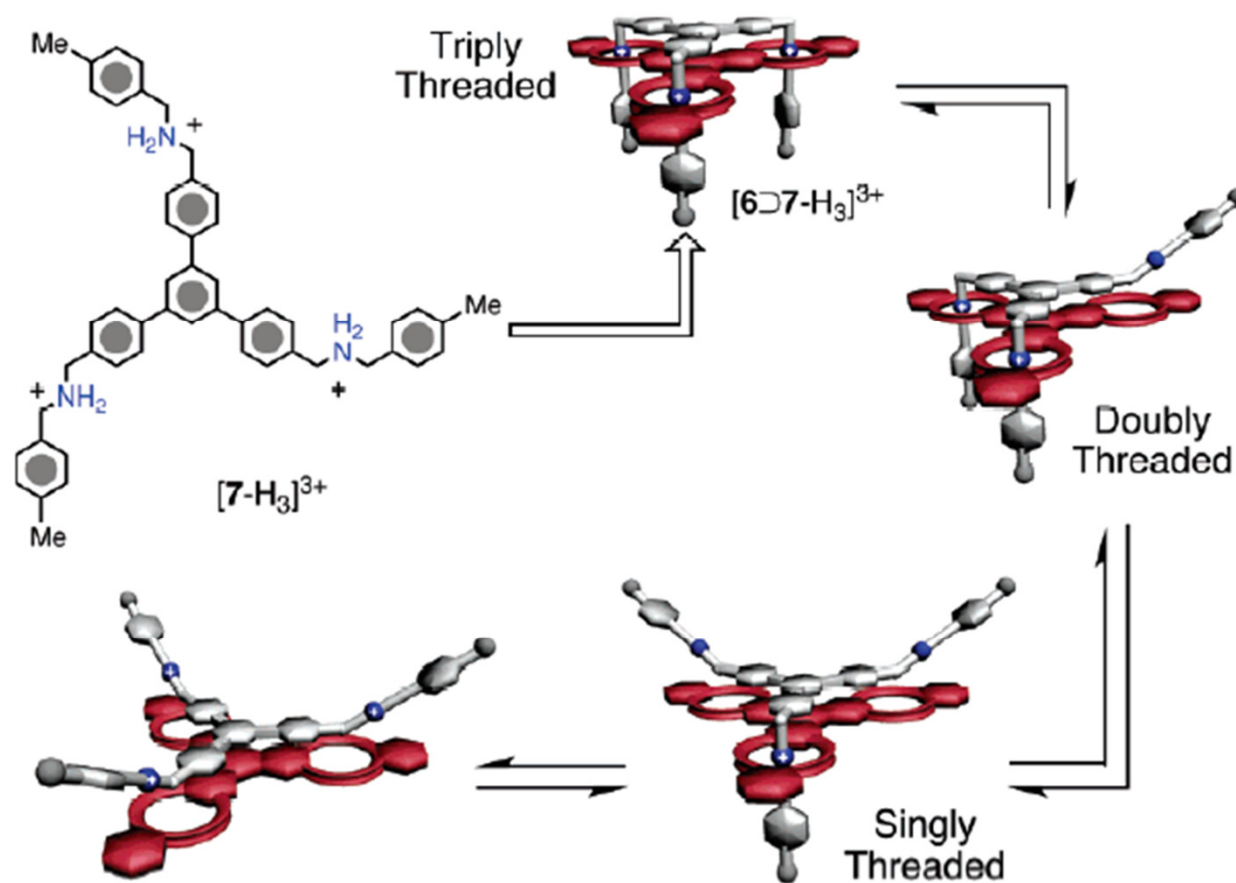
Multivalency: Kinetics of Threading Reaction

Multivalency at Surfaces

adamantane-decorated dendrimer

cyclodextrin-covered surface

(a)

multivalent binding with hosts on surface

(b) significant increase in binding constant by a factor of $\sim 10^3$
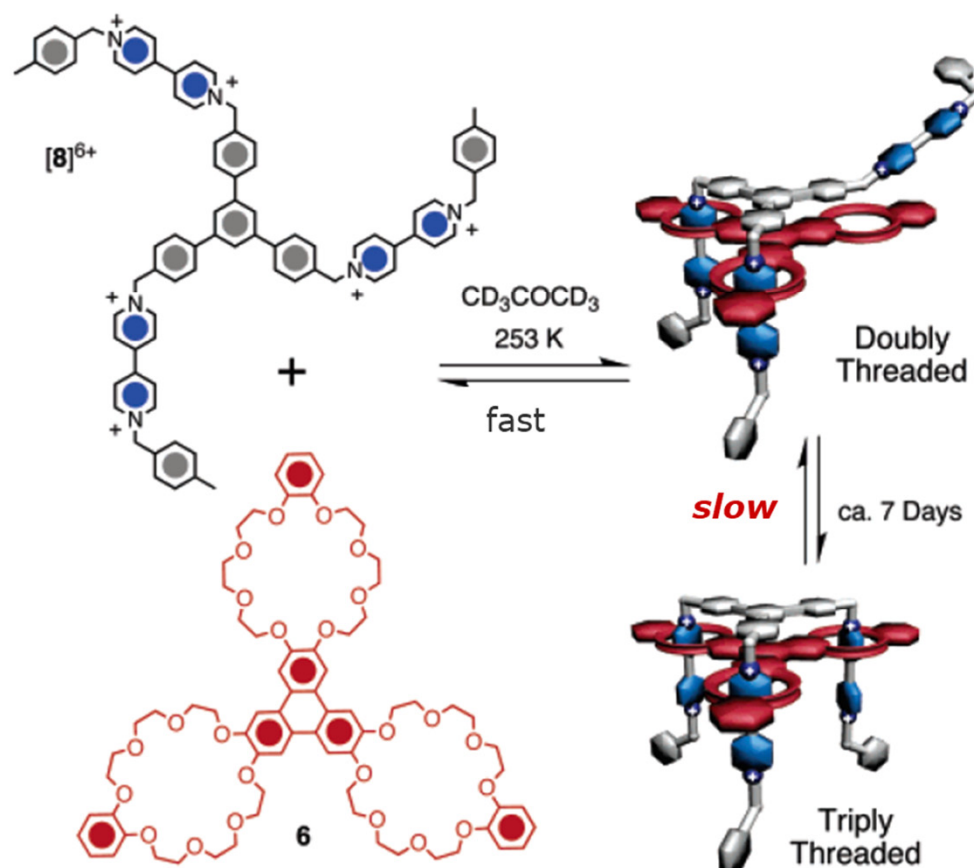
(c)

guest can be washed away with excess monovalent CDs
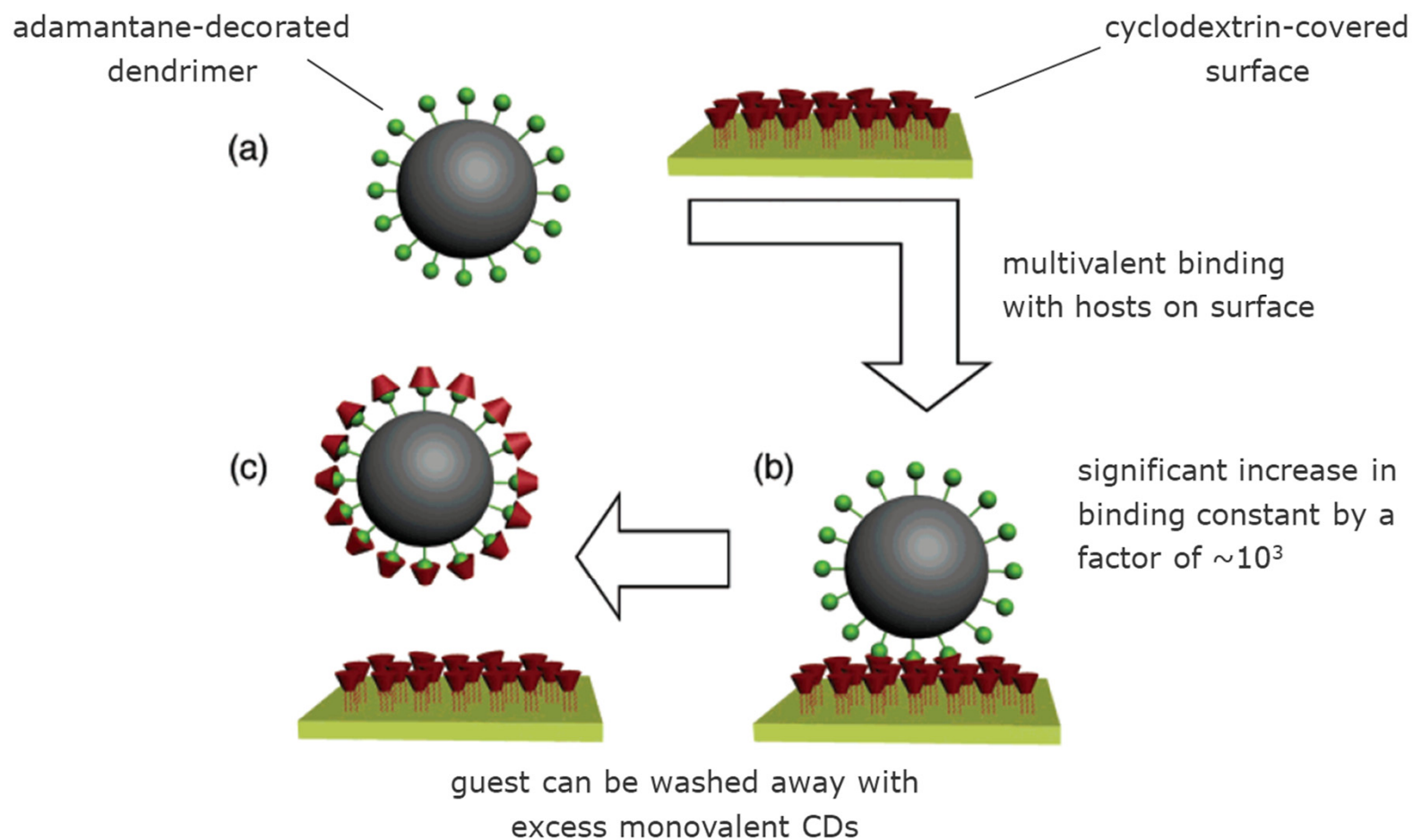
Multivalency in Biochemistry: Cholera-Toxin Inhibitors

crystal structure
of inhibitor-toxin
complex

significant increase in
binding of pentamer
relative to monomer
by a factor of $\sim 10^7$

D.R. Bundle et al., *Nature* **2000**, *403*, 669
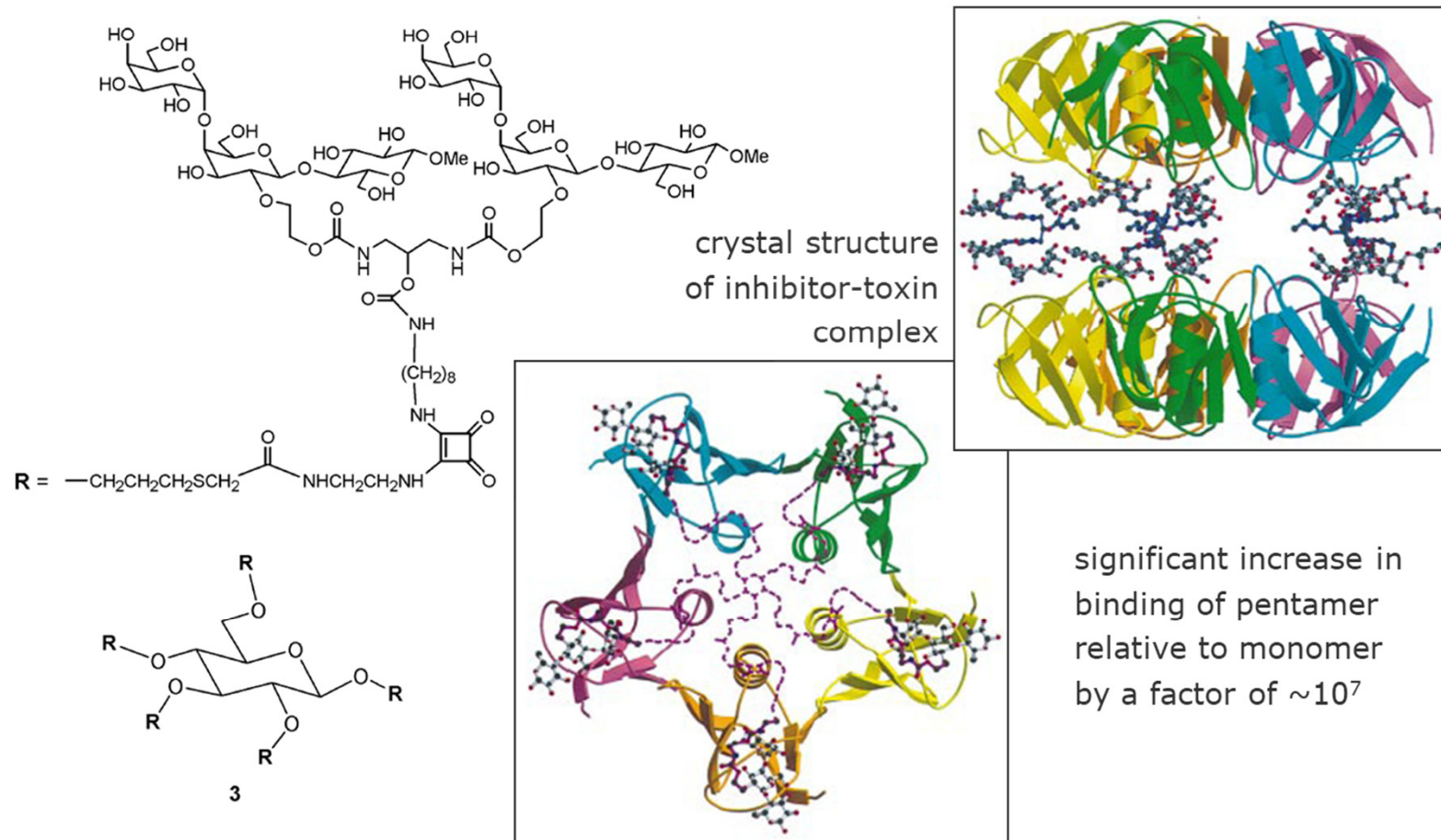
Cholera-Toxin Inhibitors: A More Detailed Analysis

$IC_{50}(\mathbf{1})/IC_{50}(\mathbf{3}) = 8.8*10^6 \text{ M}$

$IC_{50}(\mathbf{1}) = 2.1*10^{-3}\text{M}$

$IC_{50}(\mathbf{3}) = 2.4*10^{-10} \text{ M}$

$R = -CH_2CH_2CH_2SCH_2 \overset{O}{\underset{}{\overset{\parallel}{C}}} NHCH_2CH_2NH$
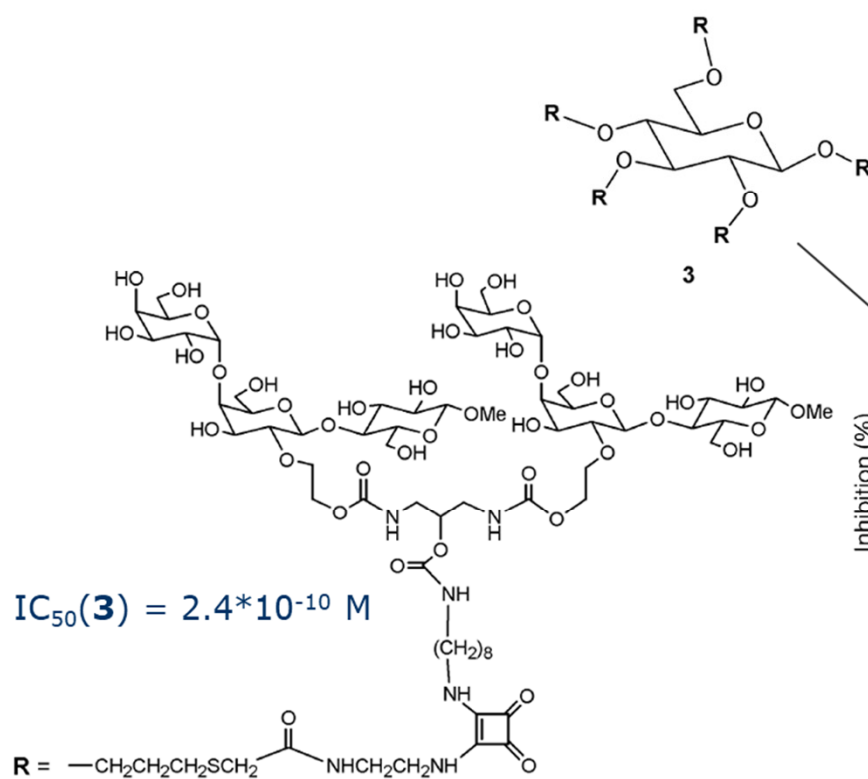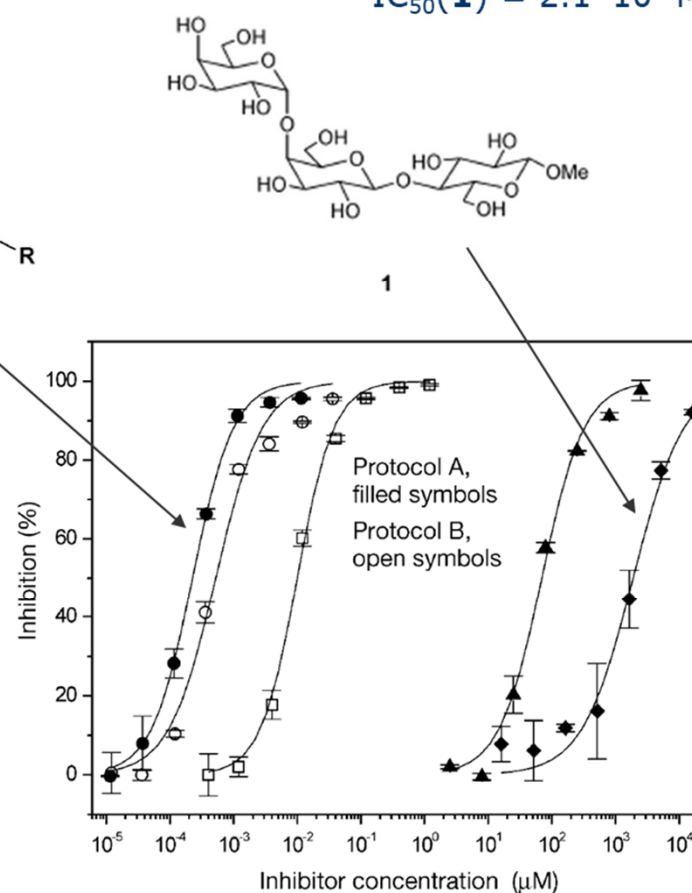
Self-Assembly and Self-Organization

How does an Ant Nest Work?

no hierarchies – individual ants do not have an overview of the organization of their states/nests

small, **simple subunits** (ants) genetically **programmed** to fulfill its tasks

short-range communication (pheromones) regulates local generation of structures (positive and negative feed-back loops)

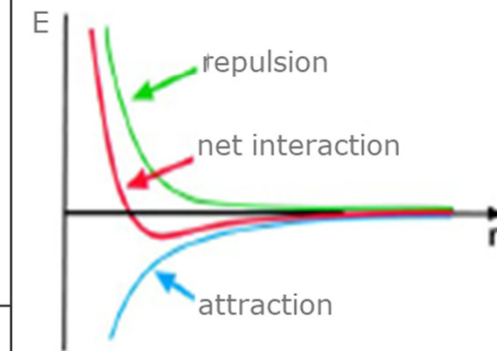subunits **mobile** and **exchangeable**

self-organization generates complexity and function

W. Kirchner, „Ameisen", Beck, 2001

Principles of Self-Assembly

Why Self-Assembly?

- Importance for life (membranes, protein complexes etc.)

- Importance for materials science (liquid crystals etc.)

- Useful synthetic strategy (complex species from simple building blocks)

- Components must be able to interact to generate order

- Interactions weak (non-covalent) and complementary; balance between attractive and repulsive interactions

- Reversibility ensures adjustability (error correction)

- The environment is important, usually solution or interface, e.g. between solution and air

- Components must be mobile (Brownian motion, agitation)
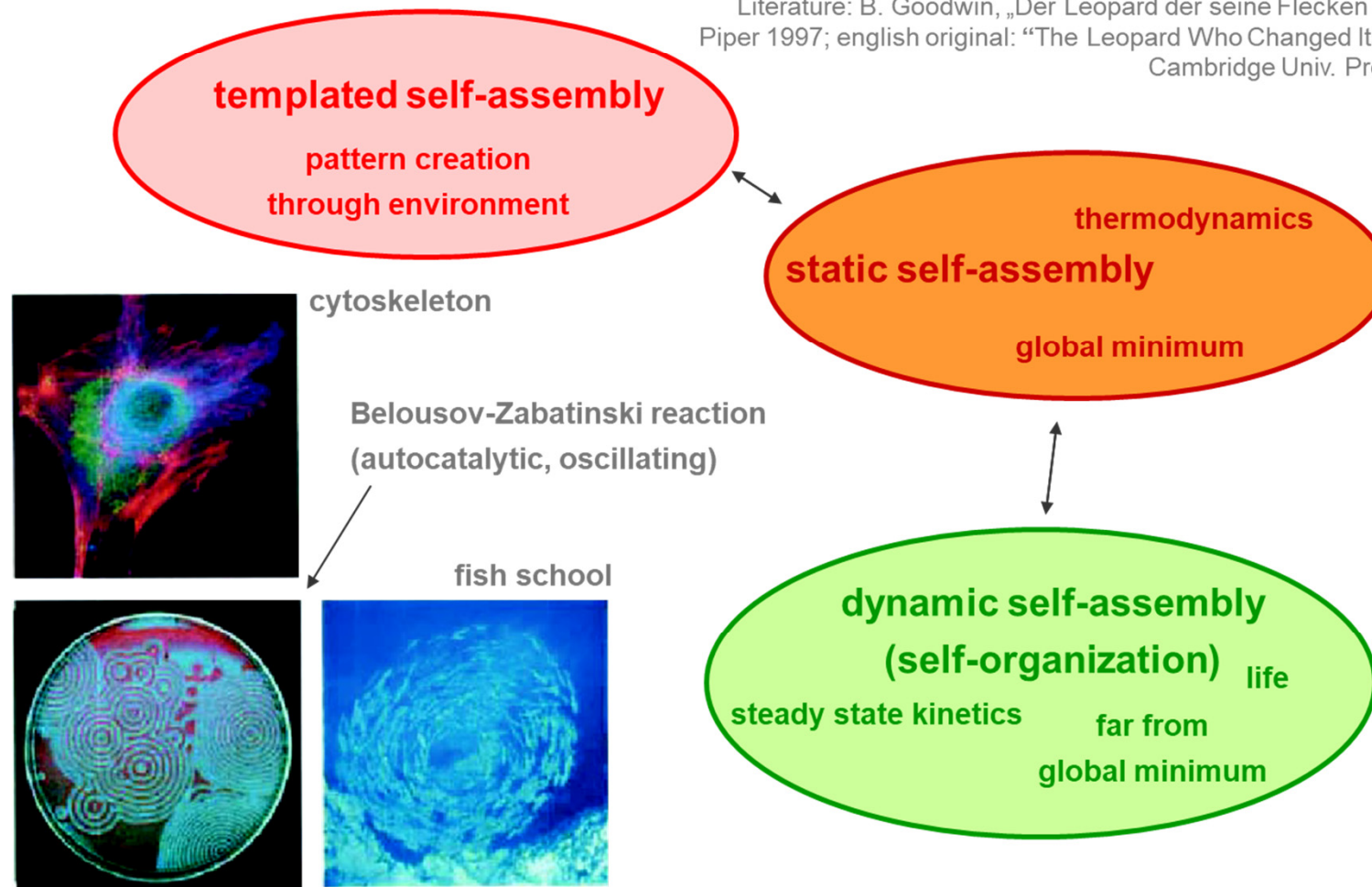

Irreversibility gives glasses
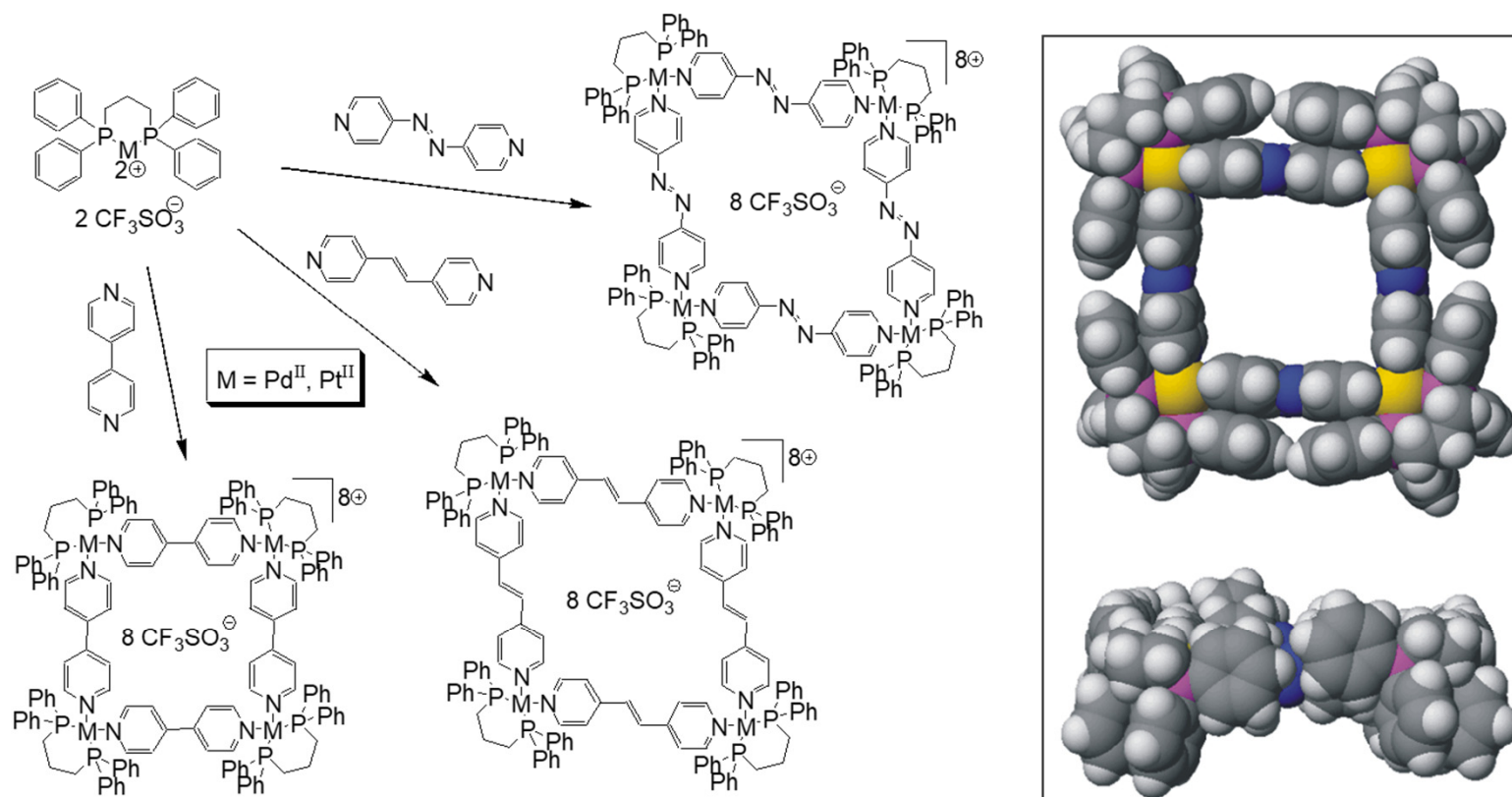
Reversibility gives crystals

Types of Self-Assembly

templated self-assembly

pattern creation through environment

static self-assembly

thermodynamics

global minimum

cytoskeleton

Belousov-Zabatinski reaction (autocatalytic, oscillating)

fish school

dynamic self-assembly (self-organization) life

steady state kinetics far from

global minimum

Stang-Type Self-Assembling Squares

$M = Pd^{II}, Pt^{II}$

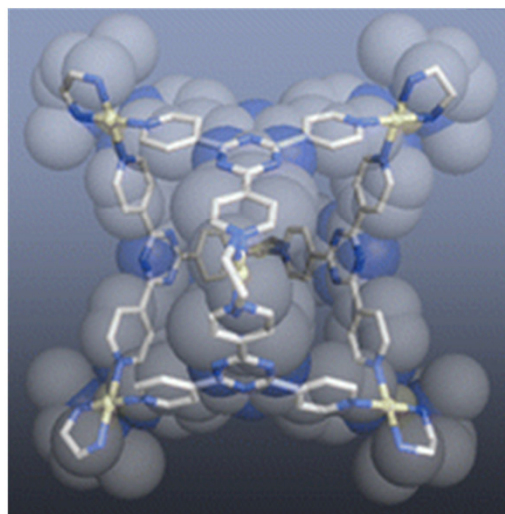C. A. Schalley, T. Müller, P. Linnartz, M. Witt, M. Schäfer, A. Lützen, *Chem. Eur. J.* **2002**, *8*, 3538
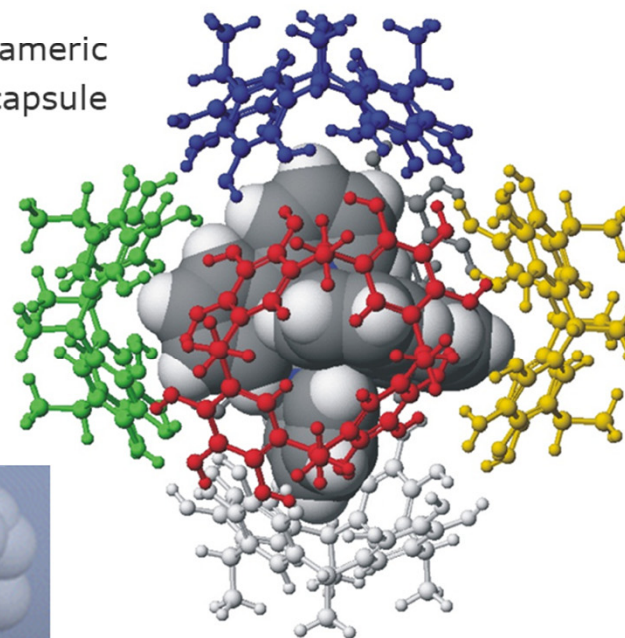
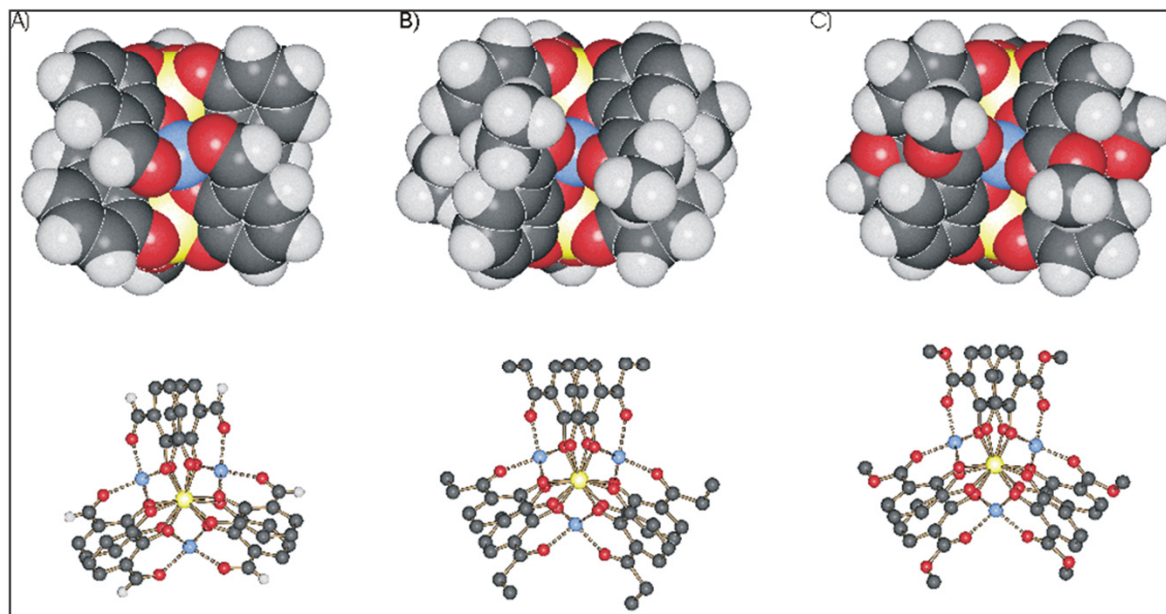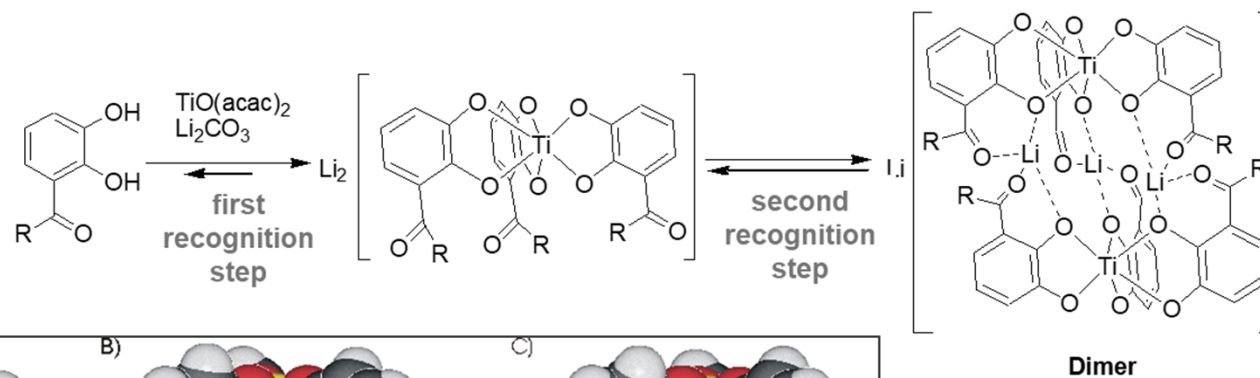# Self-Assembly through Metal Coordination or Hydrogen Bonds
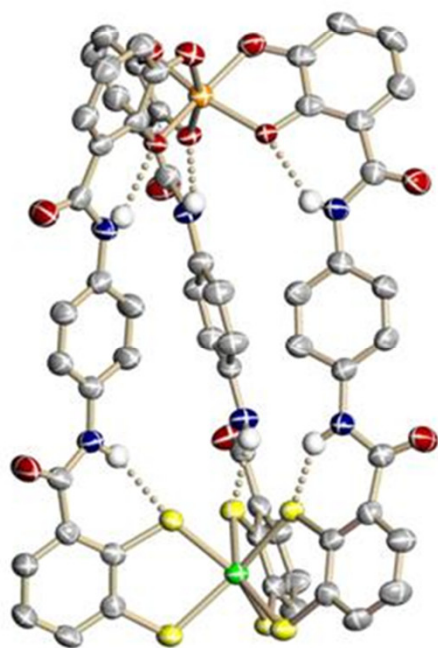
triple-stranded helicate
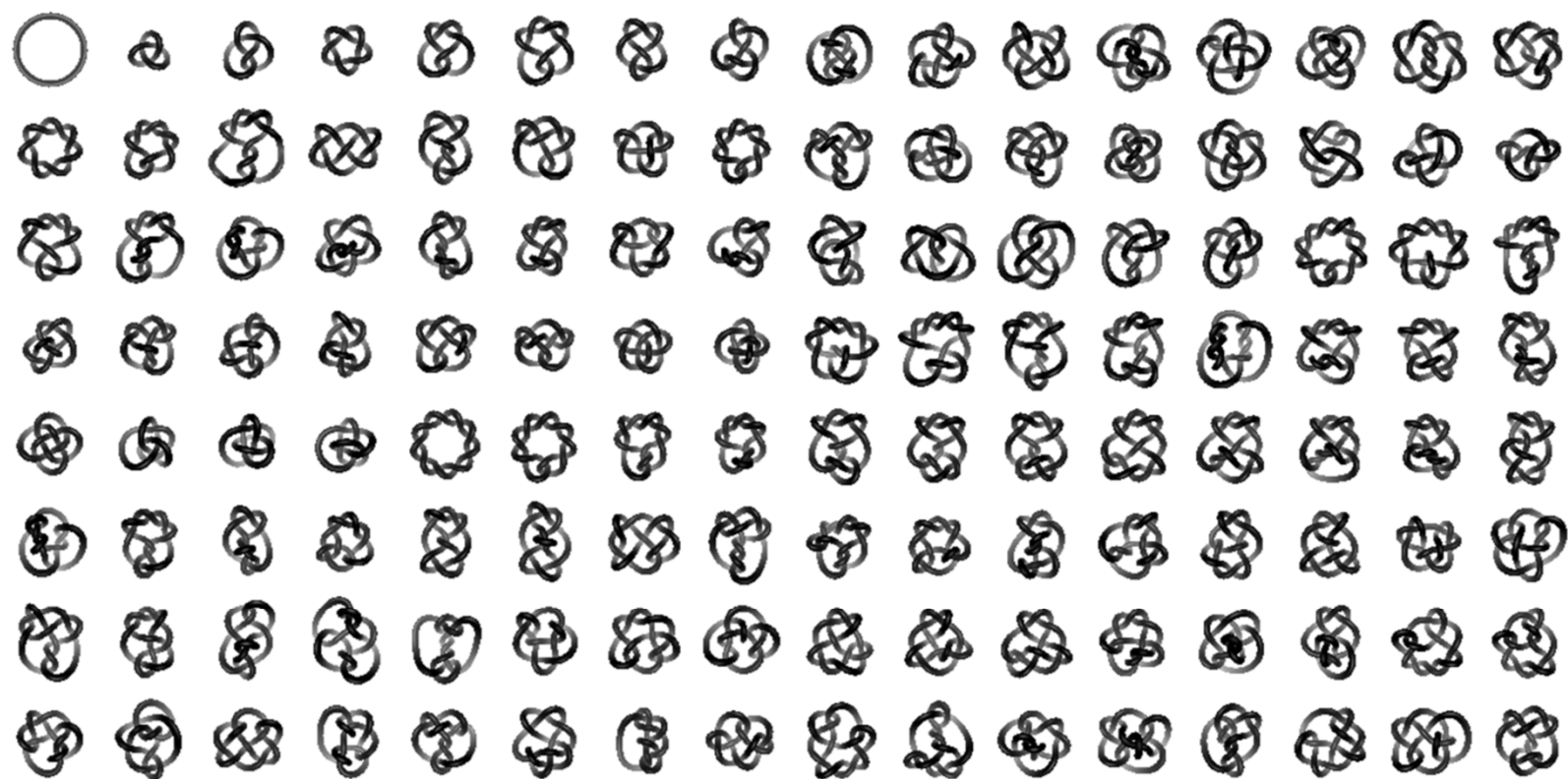
H-bonded hexameric
pyrogallarene capsule

metallo-supramo-
lecular cage
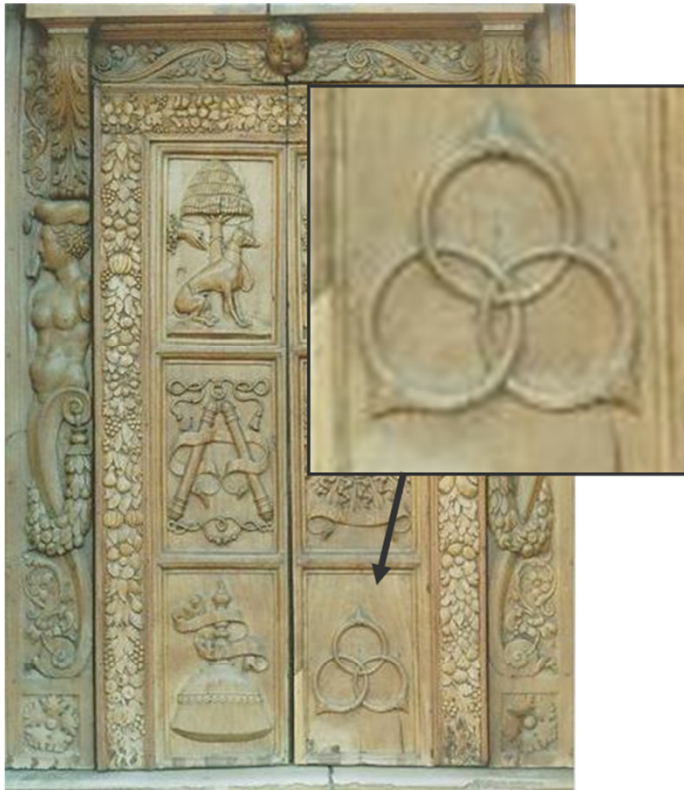
Self-Assembly in Solution: Lithium-Bridged Helicates

M. Albrecht, et al.,
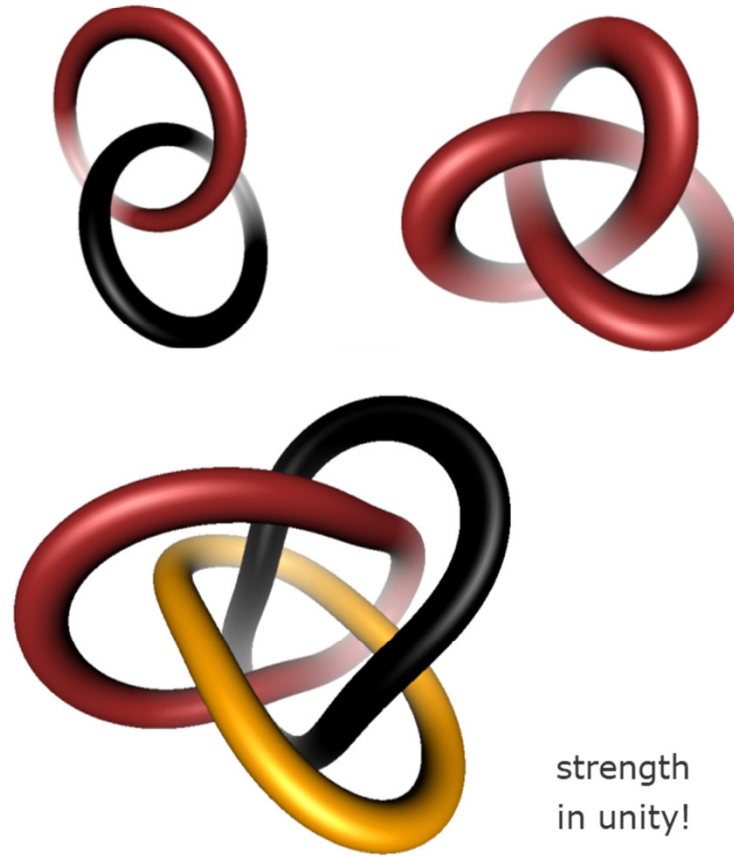*J. Am. Chem. Soc.* **2005**, *127*, 10371

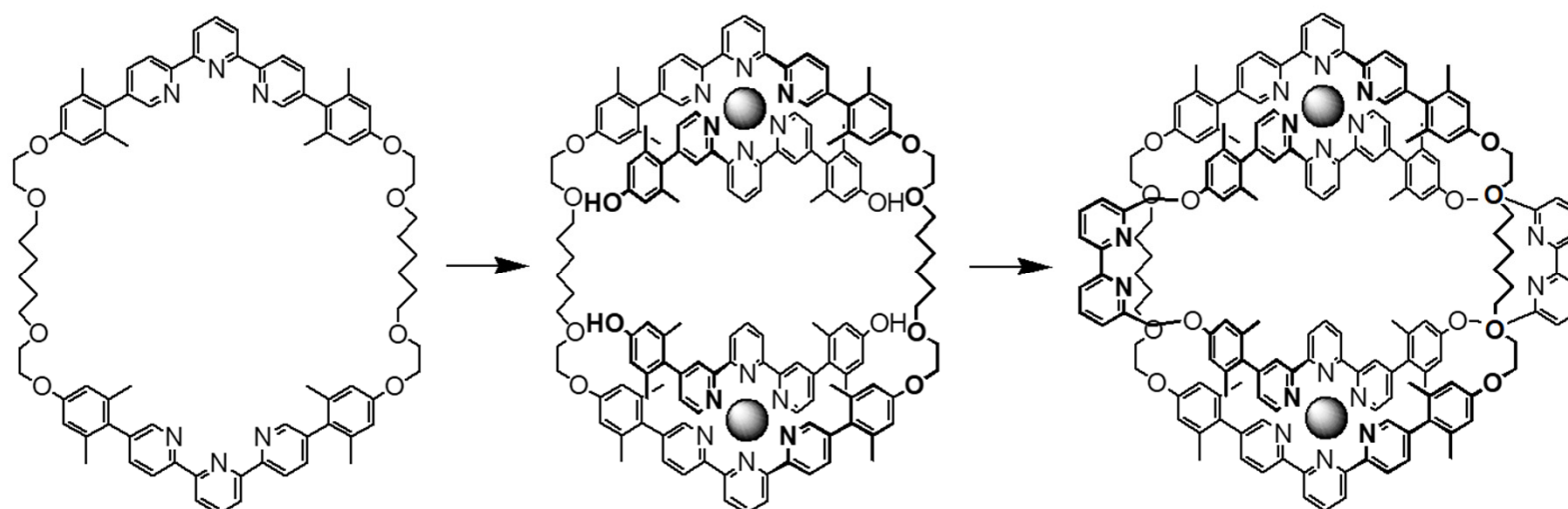The Mathematical Knot Zoo

Borromean Rings: A Synthetic Challenge

door to San Sigismonda in Cremona
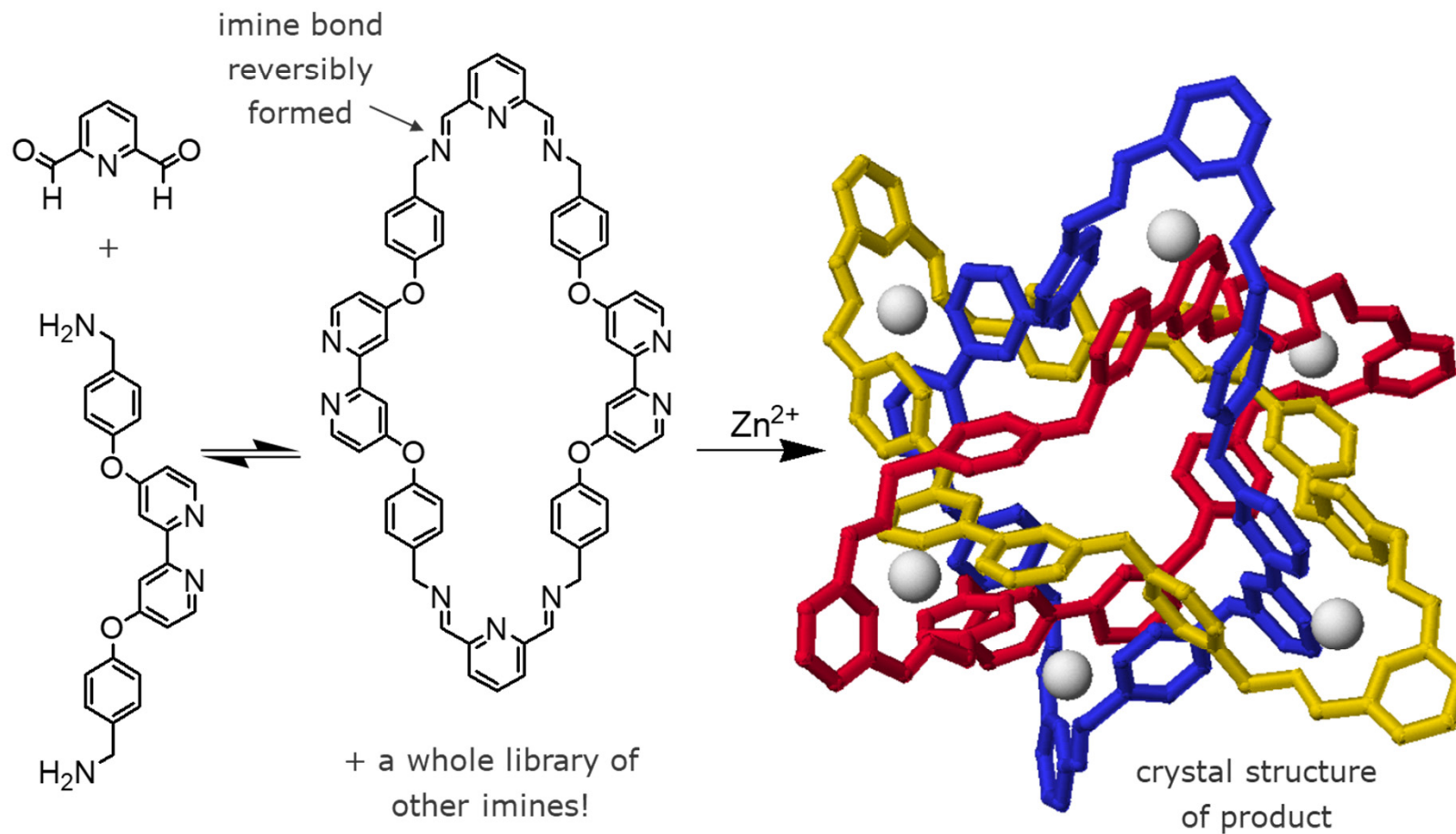(Paolo & Guiseppe Sacca, 1542)

strength
in unity!

inserting the last ring failed unfortunately

no straightforward control of the last threading step

J. C. Loren, M. Yoshizawa, R. F. Haldimann, A. Linden, J. S. Siegel, *Angew. Chem. Int. Ed.* **2003**, *42*, 5702

Self-Assembly of Borromean Rings: A One-Pot Synthesis

imine bond reversibly formed

+ a whole library of other imines!

Zn^{2+}

crystal structure of product

K.S. Chichak, S.J. Cantrill, A.R. Pease, S.-H. Chiu, G.W.V. Cave, J.L. Atwood, J. F. Stoddart, *Science*, **2004**, *304*, 1308
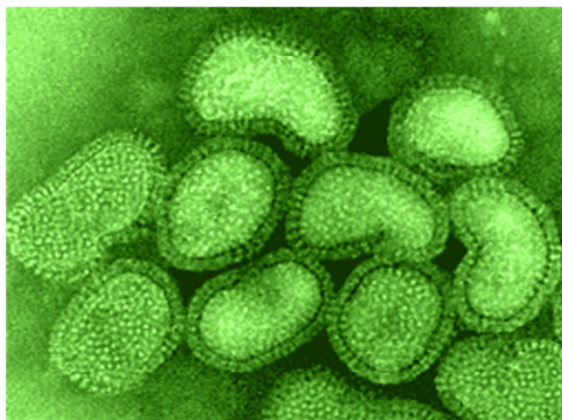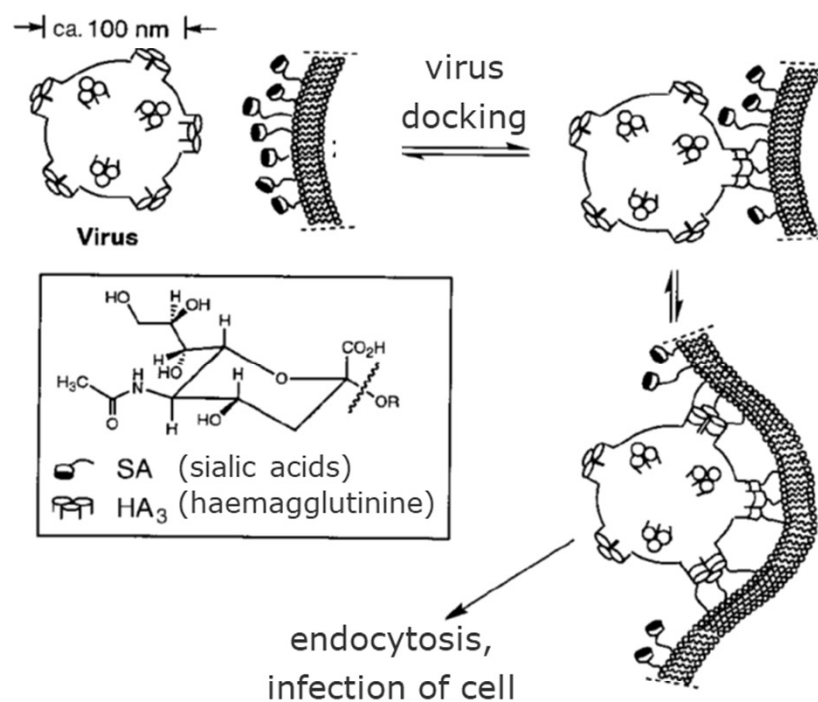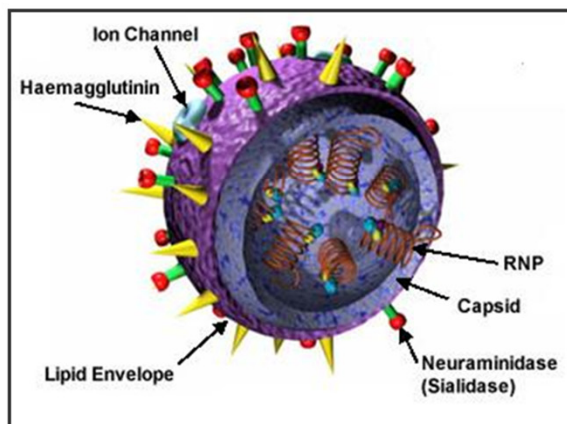
How Nature makes Use of the Concepts of Supramolecular Chemistry

Molecular Recognition Inspired by Biology: Multivalency

influenza virus

ca. 100 nm

Virus

virus docking

SA (sialic acids)

HA$_3$ (haemagglutinine)

endocytosis, infection of cell

multivalency significantly increases binding energy and initiates endocytosis

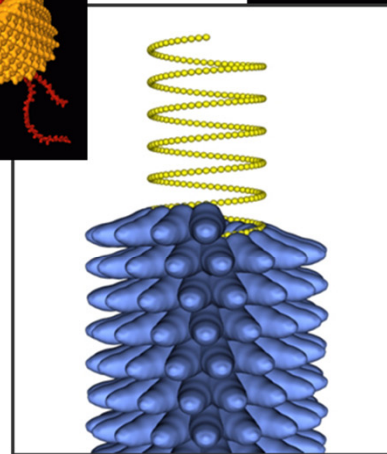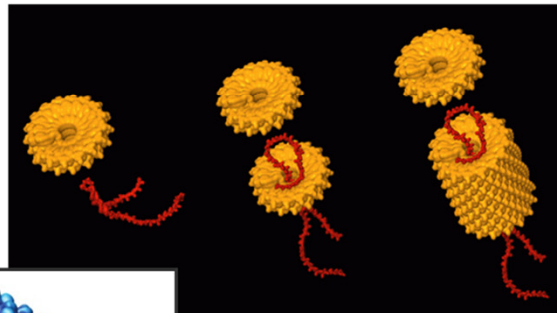M. Mammen, S.-K. Choi, G.M. Whitesides, *Angew. Chem. Int. Ed.* **1998**, *37*, 2755

Molecular Architecture Inspired by Biology: Virus Coats

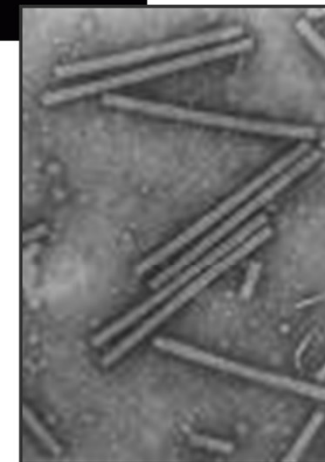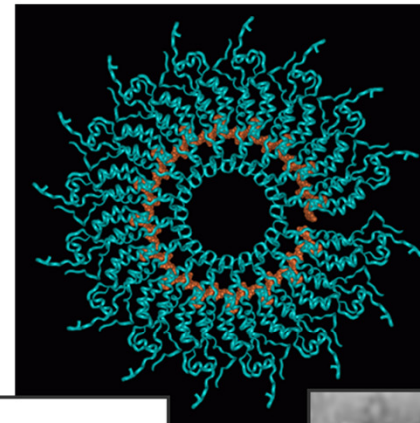virus coats **self-assemble** from many identical protein subunits

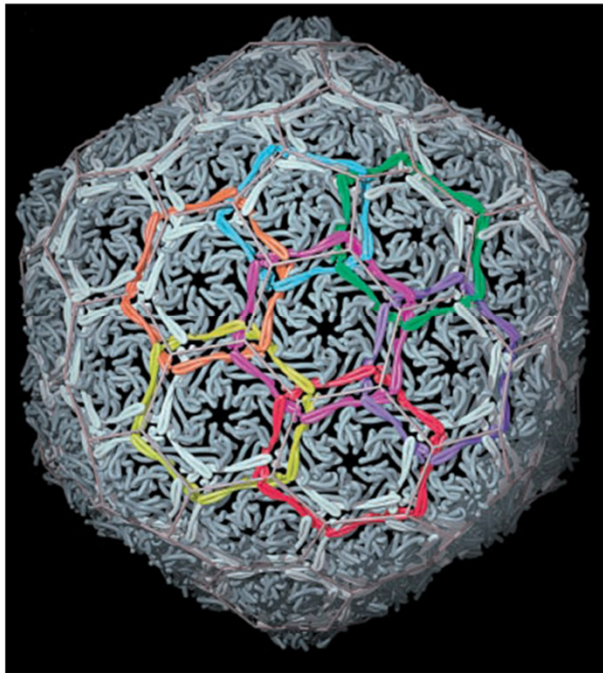TMV: RNA acts as a **template** to organize the proteins
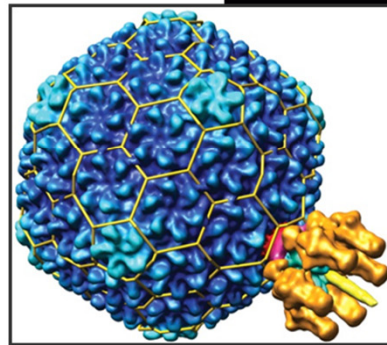
bacteriophage

tobacco mosaic virus
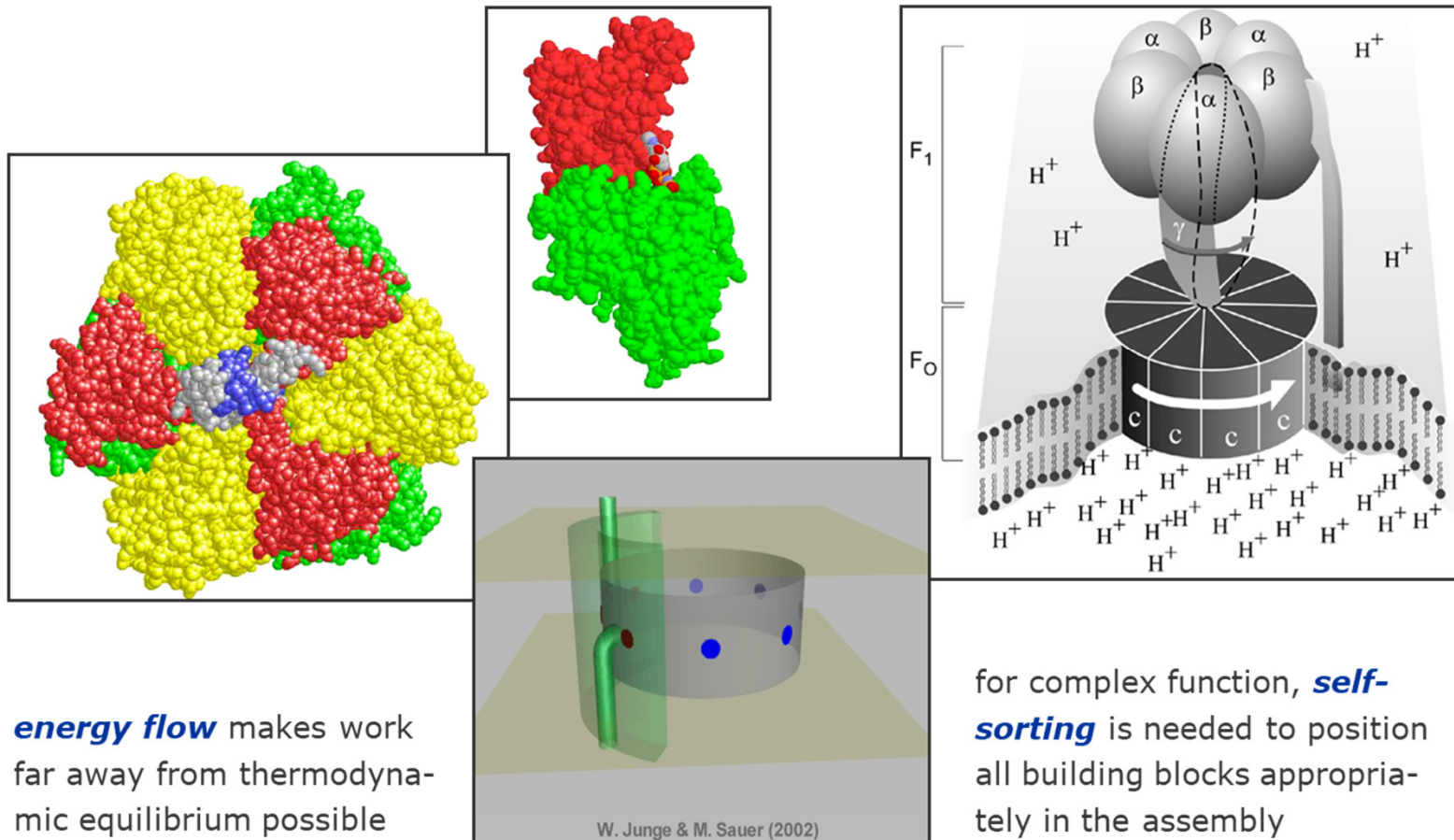

EM image

Interlocked Molecules in Nature

catenated virus coats: the chainmail
armor of bacteriophage HG97

knotted DNA: type II
topoisomerases can form knots

Function Inspired by Biology: ATP-Synthase

energy flow makes work far away from thermodynamic equilibrium possible

for complex function, *self-sorting* is needed to position all building blocks appropriately in the assembly

W. Junge & M. Sauer (2002)

P. D. Boyer, *Angew. Chem.* **1998**, *110*, 242; J. E. Walker, *Angew. Chem.* **1998**, *110*, 2438